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Long-Term Heavy Recreational Cannabis Use and Serum Delta-9-Tetrahydrocannabinol Levels are not Associated with an Impaired Liver Function in Cannabis Dependents

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ABSTRACT

To shed more light on the influence of chronic cannabis use on liver function, we performed a post-hoc analysis of routine lab data of 42 inpatient treatment-seeking (9 female, median: 27 years old) pure cannabis dependents. Serum liver function tests (LFT: transaminases, bilirubin), C-reactive protein (CRP), carbohydrate-deficient transferrin (CDT), and body mass index (BMI) were considered. The LFT were correlated with CDT, BMI, and cannabis-related clinical data (CR); i.e., the serum levels of delta-9-tetrahydrocannabinol (THC) and its major metabolites 11-hydroxy-delta-9-tetrahydrocannabinol (THC-OH) and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH), plus the cannabis-history data. The LFT was normal in 32 (76.2%) patients. There was no significant association of LFT with BMI, CRP, CDT, and CR. No significant differences were found between the group with elevated LFT (N = 10) and the group without elevated LFT (N = 32) regarding BMI, CRP, CDT, and CR, except for THC-OH, which was even lower in the elevated-LFT group. These results argue against a relevant harmful impact of chronic cannabis inhalation on the liver function of relatively healthy humans (apart from nicotine dependence). Specifically, the liver function tests were not significantly influenced by THC and THC-COOH levels, both objective markers for the amount and duration of prior cannabis use.

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Introduction

Cannabis is the most commonly used illicit drug worldwide, with an estimated level of 183 million people having used this drug in 2014, and there is an ongoing trend to liberalize or legalize its cultivation, marketing, and possession in America, Europe, and Australasia for medical and, in some countries, for recreational purposes (Pacula, Jacobson, and Maksabedian 2016; UNDOC 2017). Apart from contaminations, cannabis use is not associated with acute hepatotoxicity (Nada, Abdel-Salam, and Sleem 2017). However, daily cannabis use was identified as an independent predictor of rapid fibrosis progression and steatosis severity in untreated patients with Hepatitis C, and attenuated the success of antiviral treatment (Hézode et al. 2008). Rodent models of nonalcoholic fatty liver disease (NAFLD) found that a stimulation of hepatic cannabinoid (CB) 1-receptors had a steatogenic effect and an antagonism of CB1-receptors reversed liver steatosis, even during high caloric intake (Hézode et al. 2008; Nada, Abdel-Salam, and Sleem 2017). This was supported in liver cells from patients with alcoholic fatty liver disease (Nada, Abdel-Salam, and Sleem 2017; Patsenker et al. 2011). Activation of CB2-receptors was thought to be hepatoprotective (Nada, Abdel-Salam, and Sleem 2017).

Most recently, a cross-sectional study based upon a nationwide database of hospitalized patients in the United States described cannabis use as being associated with a reduced prevalence of NAFLD, and this effect was most pronounced in dependent cannabis users in comparison to non-dependent users who, in turn, had less NAFLD than non-users (Adejumo et al. 2017). Lifestyle and socioeconomic factors might have biased this finding (Adejumo et al. 2017). In chronic cannabis users, the liver enzymes are sometimes

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elevated (Nada, Abdel-Salam, and Sleem 2017). Usually, these people have also used other substances of abuse or follow an unhealthy lifestyle, increasing the risk of fatty liver. Thus, the influence of regular cannabis consumption on liver function needs to be studied more specifically.

We undertook a post-hoc analysis of our studies on a sample of chronic cannabis dependents who had no evidence for additional problematic substance use upon admission, apart from smoking nicotine (Bonnet et al. 2015, 2014). This analysis should provide information about possible influences of the main psychoactive constituent of cannabis; that is, the CB1-receptor agonist delta-delta-9-tetrahydrocannabinol (THC) (Busquets-Garcia et al. 2015), and its major metabolites 11-hydroxy-delta-9-tetrahydrocannabinol (THC-OH) and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) (Musshoff and Madea 2006), on liver function.

Methods

The data were collected from 2006 to 2011 from patients who were voluntarily admitted to inpatient detoxification treatment, inter alia, for their problematic cannabis use (Bonnet et al. 2015, 2014). The treatment was conducted in a specialized detoxification unit of the psychiatric ward of the University of Duisburg-Essen, Germany.

In the present analysis, patients were included who (1) were (apart from nicotine) solely dependent on cannabis according to ICD-10 (Dilling, Mombour, and Schmidt 2004); (2) reported to have used cannabis recreationally daily or nearly daily over the last six months; (3) had consumed cannabis within 24 h before admission; (4) had no other active comorbidity requiring medication; (5) showed no positive drug screen tests except for cannabis; (6) did not report having used alcohol regularly during the last six months; (7) showed no alcohol dependence according to ICD-10 (Dilling, Mombour, and Schmidt 2004); (8) had % carbohydrate-deficient transferrin (CDT) ≤1.7 (Bergström and Helander 2008); and (9) had no history of liver disease, HIV, or hepatitis (Bonnet et al. 2015, 2014). Patients were excluded if any of these serum liver function tests (LFT) were missing at admission: alanine transferase (ALT), aspartate transferase (AST), gamma-glutamyltransferase (GGT), or bilirubin. All patients had undergone a physical examination, including the determination of their body mass index (BMI), drug urine screening, electrocardiogram (ECG) and routine lab investigation, sometimes including C-reactive protein (CRP).

For quantitative HPLC (CDT) and GC-MS-analyses (THC, THC-OH, and THC-COOH), blood had been centrifuged, and the separated plasma was frozen at −20°C and sent out to a commercial clinical chemistry laboratory (Bonnet et al. 2015, 2014). The routine lab, including the LFT, were analyzed by the certificated hospital laboratory. At times of the measurements, the accepted laboratory reference value indicative for heavy drinking (>210 g ethanol/week/man or >140 g/ethanol/week/woman) was % CDT >1.7 (sensitivity 51.1%, specificity 92.8%) (Bergström and Helander 2008). The median % CDT of the study population was 1.1 (minimum: 0:4, maximum: 1.7).

For an estimation of the psychological distress, we used the global severity index (GSI) of the SCL-90-R (Franke 2002), as well as the number of fulfilled ICD-10-dependence criteria (Dilling, Mombour, and Schmidt 2004) and the severity of the cannabis withdrawal syndrome (Cannabis Withdrawal Scale, CWS) (Bonnet et al. 2014), which were determined within the first 24 hours after admission (Bonnet et al. 2014). All clinical records included a detailed addiction history.

In this post-hoc analysis, we correlated the LFT-levels with cannabis-related data (CR), comprising serum levels of THC, THC-OH, THC-COOH, and cannabis history data (amount and duration of the prior daily use, duration of dependence, age of first use). Moreover, we considered possible confounders such as age, gender, CRP, CDT, BMI, and psychological distress.

Statistical analyses were carried out using Pearson's correlation, repeated measures analysis of variance, and Welch tests, all with significance level $p < .05$.

All patients were informed about the background and procedures and gave written consent for this study, which was approved by the local ethics committee of the University of Duisburg/Essen.

Results

The sample of this post-hoc analysis consisted of 42 adult patients (nine females) who were predominantly White (97.6%), with a median age of 27 years (Table 1). Patients reported near-daily cannabis use (median 2.5 g/d) over the last six months at least (median 36 months), and were all currently dependent on cannabis, as well as on tobacco (median 20 cigarettes/d) according to ICD-10 (Dilling, Mombour, and Schmidt 2004). All patients reported having used cannabis within the last eight hours before admission, generally via smoking joints and/or inhaling with a water pipe. Sample characteristics and laboratory results are shown in Table 1, which refers to the single LFTs.

Table 1. Population characteristics and single laboratory results of the sample.

Variables	Mean (SD)	Median	Minimum	Maximum	Normal*	Increased*
Age (years old) *N* = 42	28.7 (7.9.)	27	18	52	-	-
BMI (kg/m^2) *N* = 38	22.2 (3.3)	22	17.1	35.5	*N* = 33 (78.6%)	*N* = 5 (11.9%)
Daily cannabis use (g) *N* = 42	2.5 (1.2)	2.5	0.5	6	-	-
Duration of prior daily cannabis use (months) *N* = 42	55.4 (61.8)	36	6	360	-	-
Age of the first use ever (years) *N* = 42	15.2 (2.3)	15	9	22	-	-
Duration of ICD-10-cannabis dependence (years) *N* = 42	10.0 (6.7)	7	3	32	-	-
Number of fulfilled ICD-10-cannabis-dependence criteria (upon admission) *N* = 42	4.1 (4.0)	4	4	5	-	-
Cannabis withdrawal syndrome scale (CWS) upon admission *N* = 41	6.4 (2.7)	6	2	13	-	-
Cannabis withdrawal syndrome scale (CWS), day 2 post-cessation *N* = 41	8.7 (3.4)	10	2	16	-	-
Global Severity Index (SCL-90 R) upon admission *N* = 32	1.1 (0.6)	1.0	0	2.3	up to 0.57 = normal *N* = 10 (31.3%) (Franke 2002)	0.58 to 0.78 = increased *N* = 4 (12.5%) >0.78 = markedly increased *N* = 18 (56.2%) (Franke 2002)
Laboratory results						
AST (U/L) *N* = 42	26.0 (23)	19.5	8	158	*N* = 40 (95.2%)*	*N* = 2 (4.8%)*
ALT (U/L) *N* = 42	21.8 (7.9)	21	9	48	*N* = 40 (95.2%)*	*N* = 2 (4.8%)*
GGT (U/L) *N* = 42	31 (18.8)	24	13	87	*N* = 36 (85.7%)*	*N* = 6 (14.3%)*
Bilirubin (mg/dL) *N* = 42	0.7 (0.4)	0.7	0.26	2.21	*N* = 38 (90.5%)*	*N* = 4 (9.5%)*
CRP (mg/L) *N* = 26	4.9 (8.0)	1.9	0.2	35	*N* = 19 (76.9%)*	*N* = 7 (23.1%)*

*If compared with standard values: AST (<45 U/L), ALT (<35 U/L), GGT (<55 U/L), bilirubin (<1.1 mg/dL); CRP (<5 mg/L). Among the 42 patients, there were 32 (76.2%) without an elevation of any LFT, neither transaminases (AST, ALT, GGT) nor bilirubin.

Among the 42 patients, there were 32 patients (76.2%) without an elevation of any LFT, neither transaminases nor bilirubin. That means that 10 patients (23.8%) had at least one elevated LFT. Five patients (11.9%) showed an elevated level of only one transaminase, and in one patient (2.4%), all three transaminases were increased. Furthermore, four patients (9.5%) showed increased bilirubin levels, which were associated with normal transaminases in each case. The magnitude of the raised LFT is shown in Table 2.

There was no statistically significant association of LFT levels with any CR. Excluding the four patients with elevated bilirubin levels did not change this result. Moreover, there were no statistically significant differences between the group with elevated LFT (N = 10) and the group without elevated LFT (N = 32) with regard to the serum THC and THC-COOH levels (Table 3), as well as with regard to age, gender, BMI, CRP, CDT, severity of cannabis withdrawal syndrome, psychological distress, and cannabis history data (data not shown). In the elevated LFT group, the serum THC-OH-levels were significantly lower than in the group with normal LFT (p = 0.03) (Table 3).

Table 2. Magnitude of the elevated liver function tests relative to the upper limit of normal (ULN)*.

	ALT (*N*)	AST (*N*)	GGT (*N*)	Bilirubin (*N*)
>2x ULN	0	1 (=158 U/L)	0	1 (=2.21 mg/dL)
>3x ULN	0	1 (=158 U/L)	0	0

*ULN: AST (45 U/L), ALT (35 U/L), GGT (55 U/L), bilirubin (1.1 mg/dL).

Discussion

Within this sample of chronic cannabis-dependent adults, we did not find reliable evidence of a relationship between cannabis-related data (CR) and liver function tests (LFT). Further, there was no association between the LFT and the serum levels of the CB1-receptor agonist THC and its non-psychoactive metabolite THC-COOH, which are both known to be positively related to the amount (THC) and long-term duration (THC-COOH) of the cannabis used before the determination of these biomarkers (Musshoff and Madea 2006). The serum level THC-OH, which is

Table 3. Serum cannabinoid levels: Comparison between patients with elevated LFT and normal LFT according to the Welch tests.

	Normal LFT					Elevated LFT					
Variables	Mean (SD)	Minimum	Maximum	Median	*N*	Mean (SD)	Minimum	Maximum	Median	*N*	*p*-value
THC (ng/mL)	15.1 (26.7)	2,7	139.7	7.3	26	9.7 (8.8)	3.0	31.1	6.2	9	.38
THC-OH (ng/mL)	5.5 (9.5)	.0	50.0	3.0	27	1.3 (1.0)	.0	3.1	1.3	10	**.03**
THC-COOH (ng/mL)	141.0 (162.2)	.9	741	88.5	31	106.7 (109.9)	.9	383	67.9	11	.44

positively related to the amount of recent cannabis use (Bonnet et al. 2014), was even reduced in the group with elevated LFT. This underlines a negligible influence of cannabis itself on the LFT in our cohort. The results were not significantly biased by patients who had falsely recollected cannabis use prior to admission, since all probes being evaluated had significant levels of THC and/or THC-COOH. Moreover, the findings were not influenced by age, gender, BMI, CRP, CDT, severity of cannabis withdrawal syndrome, or psychological distress. Four patients showed increased bilirubin levels which were not associated with elevated transaminases and, thus, were attributed to originate from Gilbert-Meulengracht syndrome. An exclusion of these patients did not change the finding of no association between elevated transaminases and CR.

As the elevated transaminases decreased little by little throughout the detoxification treatment (data not shown here), we did not conduct ultrasonography. Thus, the elevated transaminases were most likely associated with the circumstances of cannabis use. However, it is not known whether this was due to the cannabis use itself or a consequence of concomitant lifestyle factors prior to admission, which may have changed due to the daily structure of inpatient treatment, although this latter assumption is more likely regarding the lack of relationship between LFT and CR. Alcohol as a confounding factor cannot be ruled out because biomarkers such as CDT, used to find evidence of alcohol dependence, lack specificity and sensitivity for this purpose (Bergström and Helander 2008; Litten, Bradley, and Moss 2010). Also, the cumulative amount of smoked cigarettes or contaminations could have influenced the results, if these factors were involved in the genesis of the LFT elevations. This, however, would further support a negligible influence of cannabis itself on the LFT elevations.

Our findings are limited because liver ultrasonography (and transient elastography) was not part of the diagnostic procedure. Therefore, we had no information about a possible contribution of liver fibrosis, which could have progressed from NAFLD, although the LFT were normal (Kälsch et al. 2015; Verma et al. 2013). Further, this study allows no conclusion about the influence of cannabis on LFT if used orally or in combination with hepatotoxic drugs such as alcohol, cocaine, heroin, amphetamines, some novel psychoactive substances, or medications (Björnsson 2016; Hohmann, Mikus, and Czock 2014; Roy and Goswami 2016). The strengths of this study are the determination of the serum levels of the cannabinoids upon admission and the opportunity to analyze a cohort of people who had no other substance dependence, apart from nicotine. This allows more specific conclusions about the impact of cannabis on liver function than is possible in naturalistic cohorts (Nada, Abdel-Salam, and Sleem 2017), because those are generally contaminated with other substance use disorders (Nada, Abdel-Salam, and Sleem 2017; Roy and Goswami 2016). While naturalistic cohorts are normally easier to obtain and much larger than our sample, it took five years to find and include 42 patients who had no relevant comorbidity and who sought inpatient detoxification treatment for cannabis use only, considering that the detox ward is located in a metropolitan area and performs over 500 detoxification treatments per year. However, our findings are still limited by the small sample size, which might have failed to include people who would have been constitutionally more vulnerable to a putative cannabis-induced hepatotoxicity.

Altogether, the present study did not confirm a relevant harmful impact of chronic cannabis inhalation on the liver function of physically healthy adults (apart from nicotine dependence). This finding may change in consideration of modern consumption techniques, such as dabbing THC concentrates (Krauss et al. 2015) or the intake of synthetic cannabinoids, themselves often acting as potent full-agonists on the CB1-receptor (Solimini et al. 2017), unlike THC, which is only a partial agonist at this receptor in most cells (Busquets-Garcia et al. 2015).

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