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Pharmacokinetics and Side Effects of Δ^9-Tetrahydrocannabinol and Cannabidiol in Patients with Different Stages of CKD

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Introduction: Chronic kidney disease (CKD) affects approximately 10% of the global population and is associated with a large symptom burden. Medicinal cannabis is advised against in patients with severe CKD. However, pharmacokinetic and pharmacodynamic knowledge regarding their use in patients with CKD is lacking.

Methods: We aimed to investigate the pharmacokinetics and side effects of a single dose of Sativex, corresponding to 5.4 mg Δ^9-tetrahydrocannabinol (THC) and 5 mg cannabidiol (CBD), in patients with CKD stages 4 and 5 compared with healthy volunteers (controls). The study was a nonrandomized and unblinded clinical study.

Results: Twenty controls and 29 patients with CKD completed the study. The area under the curve (AUC) for THC (median [interquartile range]) was 2.76 (1.77–3.48), 4.16 (3.35–5.28), and 4.31 (3.16–5.42) h × ng/ml for controls, and for patients with CKD stages 4 and 5, respectively, with significant differences between patients with CKD and controls. AUC for CBD and metabolites, and other pharmacokinetic parameters, such as maximum concentration (C_{max}) and excretion of metabolites in urine were also significantly different between patients with CKD and controls. After 1.5 hours, numeric rating scale (NRS) scores for dizziness were significantly higher for each CKD group compared with controls (mean NRSscores: 0.7 and 1.5 vs. 0.1).

Conclusion: Total exposure to THC, CBD, and metabolites was higher in patients with CKD stages 4 and 5 compared with controls, and side effects may be more pronounced; however, the intersubject variability was high. If cannabis products are administered to patients with severe CKD, caution is needed.

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CKD, and particularly severely decreased kidney function, are associated with a large symptom burden including fatigue, pruritus, anorexia, pain, sleep disturbances, anxiety, nausea, restless legs, and muscle cramps.[1,2] Treatment options for this symptom complex are often not effective, and the quality of life is low and comparable with patients with metastatic cancer.[1-3]

The global prevalence of CKD is estimated to 9.1%, of which CKD stage 3 to 5 accounts for 4.1%.[4] Therefore, CKD has a major impact on global health, with approximately 700 million people living with CKD and 2.6 million deaths each year from CKD or cardiovascular disease attributable to CKD.[4] Kidney diseases are listed by the World Health Organization as the ninth leading cause of death globally.[5]

In recent years, there has been a growing interest in medical use of cannabis and cannabinoids, also in the context of symptom management in CKD.[6-10] Canadian surveys have shown that cannabis is used by patients with CKD, often without the physicians' knowledge,[11-13] which can be unfortunate because of a risk of cannabis-drug interactions.[14,15] Surveys of Canadian nephrologists have shown that they generally support use of cannabinoids for symptom management in patients with CKD and support enrolling patients for clinical trials with cannabis.[16,17] Approximately 10%

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of the nephrologists reported that they currently prescribed cannabis products for their patients, most often for chronic pain, cachexia, and nausea and vomiting.[17] However, the evidence for the effect of cannabinoids on the symptoms associated with CKD is sparse, although studies in other populations may support a potential role of cannabinoids in the treatment of symptoms experienced in CKD such as nausea, anorexia, neuropathic pain, restless legs, pruritus, sleep disturbances and anxiety.[6,8,10,18-20] Furthermore, as per the Kidney Disease Improving Global Outcomes 2024 guidelines for the evaluation and management of CKD, topical cannabis can be considered in uremic pruritus,[2] where a small open label study has suggested positive effect.[21]

THC and CBD are the most studied cannabinoids and are present in medications with a marketing authorization, such as Sativex (Jazz Pharmaceuticals Ireland Ltd., Dublin, Ireland) and Epidiolex/Epidyolex (Jazz Pharmaceuticals Ireland Ltd., Dublin, Ireland).[22,23] THC and CBD are lipophilic compounds with large distribution volumes and a high degree of plasma protein binding.[23,24] They are metabolized by CYP-enzymes (CYP3A4, CYP2C9, and CYP2C19) to metabolites such as 11-hydroxy-THC (THC-OH), 7-hydroxy-CBD, 11-nor-9-carboxy-THC (THC-COOH), and THC-COOH-glucuronide[23,24] Metabolites are regarded both active and inactive.[23,24] Metabolites are excreted through feces and approximately 20% through urine.[22,24] Most pharmacokinetic data on cannabinoids come from studies with healthy volunteers; however, it is well-described that severe CKD can affect the pharmacokinetics and metabolism of nonrenally cleared drugs.[25,26] In patients with CKD, 1 study found that the pharmacokinetics of CBD (Epidiolex) were not influenced by kidney function and was well-tolerated; however, other authorized medications containing cannabinoids, such as nabilone (Cesamet; Bausch Health Companies Inc., Quebec, Canada), have not been investigated in CKD.[27,28]

Severe CKD is regarded a contraindication for use of medicinal cannabis in the Danish guideline for use of medicinal cannabis; according to Canadian information for health care professionals, it should not be used in patients with severe renal disease.[29,30] This may be due to lack of knowledge, which underlines the need for pharmacokinetic studies in patient-specific populations such as patients with CKD.[10,31] Furthermore, pharmacokinetic knowledge is pertinent in guiding safe dosing in the population and before studies on efficacy in CKD can be conducted.

We hypothesize that patients with CKD have a larger AUC for THC, CBD, and metabolites after a single dose of Sativex, and thereby experience more side effects compared with healthy volunteers (controls). In addition, we hypothesize that excretion of THC, CBD, and metabolites in urine is smaller in patients with CKD than in the controls.

The aim of our study was to elucidate the pharmacokinetics and occurrence of side effects for THC, CBD, and metabolites in patients with CKD stages 4 and 5 compared with controls.

METHODS

Study Design

The study was an unblinded, nonrandomized, single-dose pharmacokinetic study approved by The Danish Medicines Agency (EudraCT no. 2019-002786-35) and The Danish Research Ethics Committees, Central Region Denmark (1-10-72-142-20). The study was conducted at Department of Renal Medicine, Aarhus University Hospital, Denmark in accordance with the study protocol, the Declaration of Helsinki, the General Data Protection Regulation, and the Danish Data Protection Act. The Good Clinical Practice unit, Aarhus, Denmark, monitored the study. We reported the study in accordance with the CONSORT guideline for relevant items.[32]

Participants

Participants with CKD stages 4 and 5 were recruited from the Department of Renal Medicine, Aarhus University Hospital, Denmark, and controls were recruited by advertisement. Written informed consent was obtained from all participants. A full list of inclusion and exclusion criteria are presented in the Supplementary Material. Key inclusion criteria were aged $\geq$ 18 years and use of safe contraception. Key exclusion criteria were psychotic disorder; a family history of schizophrenia; previous suicide attempt; abuse of alcohol or drugs; treatment with benzodiazepines, benzodiazepine-like medication, opioids or warfarin; use of THC or CBD within 2 months; treatment with strong inhibitors or inducers of CYP3A4, CYP2C9, or CYP2C19, or medical products with known potential of clinically significant interaction with THC and/or CBD; unstable angina pectoris; heart failure with an ejection fraction $<$ 20%; treatment-resistant hypertension grade 3; significantly impaired liver function; pregnancy or breastfeeding; epilepsy; and allergy to the ingredients in Sativex. Study participants were included in 4 prespecified groups dependent on estimated glomerular filtration rate (eGFR) calculated with the CKD-Epidemiology Collaboration 2009 equation without race correction[33] and treatment with dialysis. Groups were as follows: (i) eGFR $>$ 60 ml/min per 1.73 m^2 (controls), (ii) eGFR $\leq$ 30 and $>$ 15 ml/min per 1.73 m^2 (CKD stage 4), (iii) eGFR $\leq$ 15 ml/min per 1.73 m^2 (CKD stage 5, not on dialysis), and (iv) CKD and

treatment with dialysis. Results for patients treated on dialysis are not reported in this publication. In addition, renal function was estimated based on cystatin C,[34] a combination of creatinine and cystatin C[34] without race correction, and as absolute eGFR (ml/min, non-indexed for body surface area), where body surface area was estimated with Du Bois equation.

Outcomes

The primary endpoint was the AUC for THC (AUC_{THC}) measured in plasma over 24 hours from administration of Sativex. Secondary endpoints included AUC for CBD, THC-OH, THC-COOH, THC-COOH-glucuronide, tetrahydrocannabinolic acid A (THCA-A), and cannabidiolic acid (CBDA) in plasma; C_{max} and time to C_{max} (T_{max}) in plasma; and total 24-hour urine excretion of THC, CBD, THC-OH, THC-COOH, THC-COOH-glucuronide, THCA-A, and CBDA. Furthermore, the prevalence of side effects was assessed on a questionnaire with the symptom burden on a NRS from 0 to 10 over 24 hours from the time of administration of Sativex. The questionnaire included questions regarding common side effects of cannabis use. The list of questions are presented in the Supplementary Material. The questionnaire was not validated in the population. One question was added after trial commencement (feeling intoxicated or high). According to the protocol, the metabolite 7-hydroxy-CBD should have been measured; however, the analysis could not be performed because of unavailability of the reference standard.

Trial Procedures and Collection of Samples

The participants had blood samples taken for analysis of renal parameters within 7 days before the study participation. The participants met at Aarhus University Hospital after 7 hours of fasting and received 2 oromucosal sprays of Sativex, corresponding to 5.4 mg THC and 5.0 mg CBD to the inside of the cheek, without any restrictions related to swallowing. The recommended starting dose of Sativex is 1 spray followed by a slow up-titration; however, CBD alone can be initiated at much higher doses.[22,23] Blood samples were drawn and NRS questionnaires were completed 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 hours after administration of Sativex. We collected urine over 24 hours from the administration of Sativex. Participants attempted to empty their bladder before starting the urine collection ($t = 0$) and again right before finishing the collection ($t = 24$). For safety reasons, blood pressure and heart rate were measured 2 hours after administration of Sativex using a single measurement with an automatic blood pressure monitor (Microlife, AG Swiss Corporation, Widnau, Switzerland). Fasting continued until 5 hours after administration of Sativex. Fluid intake was not allowed 2 hours before and 2 hours after administration of Sativex. However, medications could be taken with water, if necessary.

Sample Size

A sample size calculation, based on a previous pharmacokinetic study of 2 sprays of Sativex in healthy volunteers,[35] showed that 20 participants were required in each group (2 means) to detect a 50% change in AUC, with a significance level of 0.05, a power of 0.80, and an assumed 10% increase of the SD for patients with CKD. Owing to the basis of a small pharmacokinetic study and a high intersubject variability, 25 participants were aimed for in each CKD group and controls.

Analysis of Cannabinoids and Renal Parameters

We collected blood samples in 4 ml vacuum tubes with oxalate, and 24-hour urine in glass containers. We centrifuged blood for 10 minutes (3500 rpm and 4 °C) and froze plasma and urine in brown glass vials or PET vials at −80 °C or −70 °C; plasma was processed and frozen within 4 hours and urine after the total urine collection. We analyzed the total concentration of THC, THC-OH, THC-COOH, THC-COOH-glucuronide, THCA-A, CBD, and CBDA in plasma and urine samples by a modified version of the cannabinoid method described by Sørensen and Hasselstrøm.[36] Briefly, the major changes included the following: (i) 150 µl sample was used, (ii) volumes of organic solvents were adjusted accordingly before transfer of sample mixture to an ultrafiltration filter plate with a 30-kDa Omega membrane (Pall Corporation, Ann Arbor, MI), and (iii) subsequently the filtrate was mixed with 10 µl formic acid and eluted through an Ostro plate (Waters, Milford, MA). The final filtrate (500 µl) was evaporated and reconstituted in 100 µl 70% methanol. The analysis was performed on an ultrahigh-performance liquid chromatography-tandem mass spectrometry system (Excion UHPLC coupled to a QTRAP 6500+; Sciex, Ontario, Canada). The lower limits of quantification were 0.025, 0.1, 0.1, 0.2, 0.01, 0.03, and 0.025 ng/ml for THC, THC-OH, THC-COOH, THC-COOH-glucuronide, THCA-A, CBD, and CBDA, respectively. The relative reproducibility SDs (i.e., the day-to-day variation of independent analytical results) were in the ranges of 5% to 15% and 3% to 9% at the individual cannabinoid concentrations of 0.2 and 20 ng/ml, respectively.

Creatinine and cystatin C were measured using commercially available assays from Siemens Healthineers. The creatinine assay was traceable to the Isotope Dilution Mass Spectrometry standard, and the cystatin C assay was traceable to the International Federation of Clinical Chemistry and Laboratory Medicine standard.

Assay performance was ensured through internal and external quality controls.

Data Analysis

We collected and managed data in Research Electronic Data Capture tools[37,38] hosted at Aarhus University, Denmark, and included data from participants complying with the protocol for more than 6 hours after administration of Sativex (defined as completion of the study, Figure 1). Adverse events reported in addition to the NRS questionnaire were specified for all participants who were administered Sativex. We did not impute missing data. We performed data analysis in Stata/SE 18.0 (StataCorp LLC, College Station, TX), and graphical work in GraphPad Prism 10.2.1 (Dotmatics, Boston, MA) using the pharmacokinetic package in Stata for the noncompartmental analysis and the trapezoidal rule for calculation of AUC. If the concentration-curve reached 0, we did not include measured concentrations thereafter in the AUC calculation. Total excretion in urine was calculated from the measured concentration and the volume of the 24-hour urine.

We present data as median with interquartile range because in general, the approximation to normal distribution was poor. However, we present NRS scores as means despite nonnormal distribution because medians at several time points were 0 because of the distribution of answers in the questionnaire. We analyzed baseline data, AUC, C_{max}, and T_{max} for THC, CBD, and metabolites, differences between NRS scores (prespecified timepoints 1, 2, 4, 12, and 24 hours), and total excretion

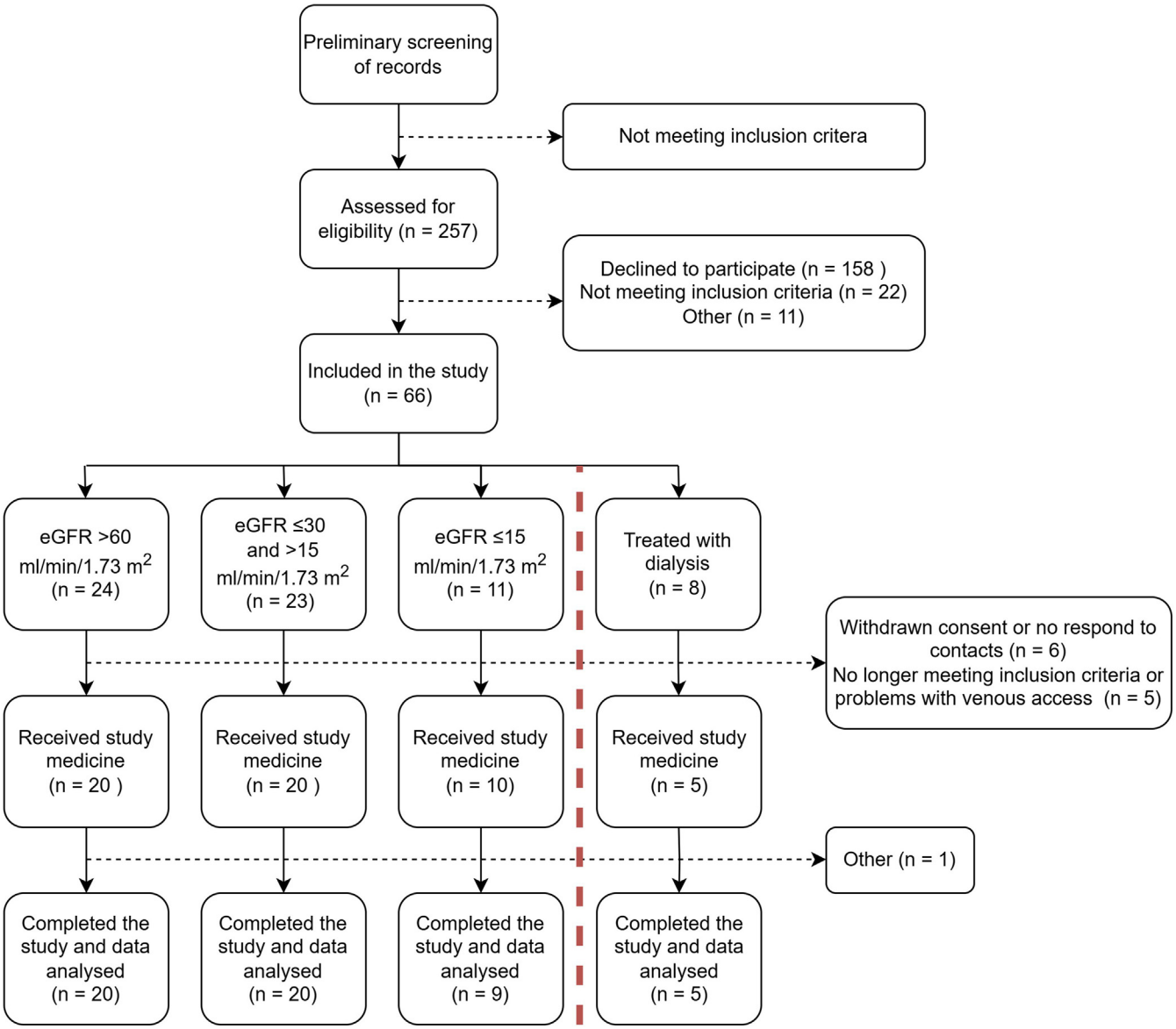

Figure 1. Participant flow. Completion of study, defined as data for more than 6 h after administration of Sativex. Data for patients treated with dialysis are not reported in this publication. eGFR, estimated glomerular filtration rate.

of cannabinoid metabolites in urine with Kruskal-Wallis test followed by Dunn's test corrected with Bonferroni or chi-square test, where appropriate.

We analyzed differences between vital parameters at baseline and 2 hours after administration of Sativex with Wilcoxon rank-sum test and performed regression analyses between renal parameters and log transformed AUC of cannabinoids to approximate normal distribution with and without adjustment for age, body mass index (BMI), and sex (male/female).

RESULTS

Participants and Baseline Characteristics

Owing to challenges with recruitment (the COVID-19 pandemic), we only included 66 participants between October 2020 and December 2023, of which 49 participants not treated with dialysis completed the study (Figure 1). The control group was younger and healthier compared with the CKD groups with a lower systolic blood pressure, a lower number of used drugs, less hypertension and ischemic heart disease, a smaller waist measurement, and a tendency to a lower BMI (Table 1). Four out of 735 planned blood samples were missing. At t = 0, all measured plasma concentrations were below the lower limits of quantification.

Noncompartmental Analysis of Pharmacokinetic Parameters

THC

In Figure 2, we show plasma concentrations of THC in the 3 groups. Each CKD group had a significantly larger AUC_{THC} and C_{maxTHC} compared with controls, whereas the difference was not significant between the 2 CKD groups (Table 2). T_{maxTHC} was significantly shorter for participants with eGFR $\leq$ 15 compared with controls

Table 1. Baseline characteristics

Characteristics	Control (n = 20)	eGFR ≤ 30 and > 15 (n = 20)	eGFR ≤ 15 (n = 9)	P value
Age, yrs	27 [23–54]	64 [45–74]	68 [61–73]	0.000
Sex: male, n (%)	12 (60)	14 (70)	8 (89)	0.295
Weight, kg	83 [74–96]	88 [74–97]	92 [75–96]	0.892
Height, cm	181 [174–188]	175 [168–180]	177 [169–180]	0.051
Body mass index, kg/m^2	24.6 [21.6–27.7]	29.2 [24.0–31.5]	27.1 [25.6–30.8]	0.143
Waist measurement, cm	92 [81–98]	102 [94–111]	103 [94–105]	0.016
Smoking, n (%)	< 3	5 (25)	< 3	0.393
Systolic blood pressure, mmHg	125 [115–140]	139 [131–150]	137 [129–153]	0.018
Diastolic blood pressure, mmHg	80 [72–89]	89 [82–93]	81 [81–90]	0.056
Heart rate, bpm	68 [61–78]	74 [64–79]	69 [62–89]	0.397
Number of drugs	1 [0–2]	8 [6–11]	7 [6–8]	0.000
Creatinine, µmol/l	76 [66–86]	256 [234–292]	437 [381–459]	0.000
Blood urea nitrogen (mmol/l)	4.6 [4.0–5.3]	16.5 [14.0–18.3]	17.4 [15.4–25.2]	0.000
Cystatin C (mg/l)	0.97 [0.80–1.08]	2.93 [2.69–3.25]	3.72 [3.49–3.82]	0.000
$eGFR_{creatinine}$[a], ml/min per 1.73 m^2	107 [95–121]	21 [18–24]	11 [11–13]	0.000
$eGFR_{cystatin\ C}$[b], ml/min per 1.73 m^2	94 [79–113]	18 [16–20]	13 [12–14]	0.000
$eGFR_{creatinine\text{-}cystatin\ C}$[c], ml/min per 1.73 m^2	98 [86–114]	19 [16–20]	12 [11–12]	0.000
Absolute $eGFR_{creatinine}$, ml/min	127 [100–139]	24 [19–26]	13 [13–14]	0.000
Comorbidities				
Diabetes[d], n (%)	0 (0)	0 (0)	<3	0.103
Hypertension[e], n (%)	<3	17 (85)	9 (100)	0.000
Obesity[f], n (%)	9 (45)	14 (70)	7 (78)	0.142
Ischaemic heart disease[g], n (%)	0 (0)	5 (25)	0 (0)	0.018
Cause of CKD				
Hypertension, n (%)		<3	3 (33)	
Obstruction, n (%)		4 (20)	<3	
Glomerulonephritis, n (%)		3 (15)	<3	
Vasculitis, n (%)		<3	0 (0)	
Hereditary, n (%)		4 (20)	3 (33)	
Others, n (%)		3 (15)	<3	
Unknown, n (%)		<3	0 (0)	

CKD, chronic kidney disease; CKD-EPI, CKD-Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate.
[a]Estimated using $CKD\text{-}EPI_{creatinine\ 2009}$[33] without correction for race.
[b]Estimated using $CKD\text{-}EPI_{cystatin\ C\ 2012}$.[34]
[c]Estimated using $CKD\text{-}EPI_{creatinine\text{-}cystatin\ C\ 2012}$ without correction for race.[34]
[d]Diagnosis of diabetes.
[e]Treatment with antihypertensives (not diuretics) unless prescribed for a clearly defined diagnosis, not being hypertension.
[f]BMI ≥ 25 kg/m^2.
[g]Known angina pectoris, myocardial infarction, percutaneous coronary intervention, or coronary-artery bypass grafting.
Presented as median [interquartile range] unless stated otherwise. The P values refer to Kruskal-Wallis test or chi-square test as appropriate.

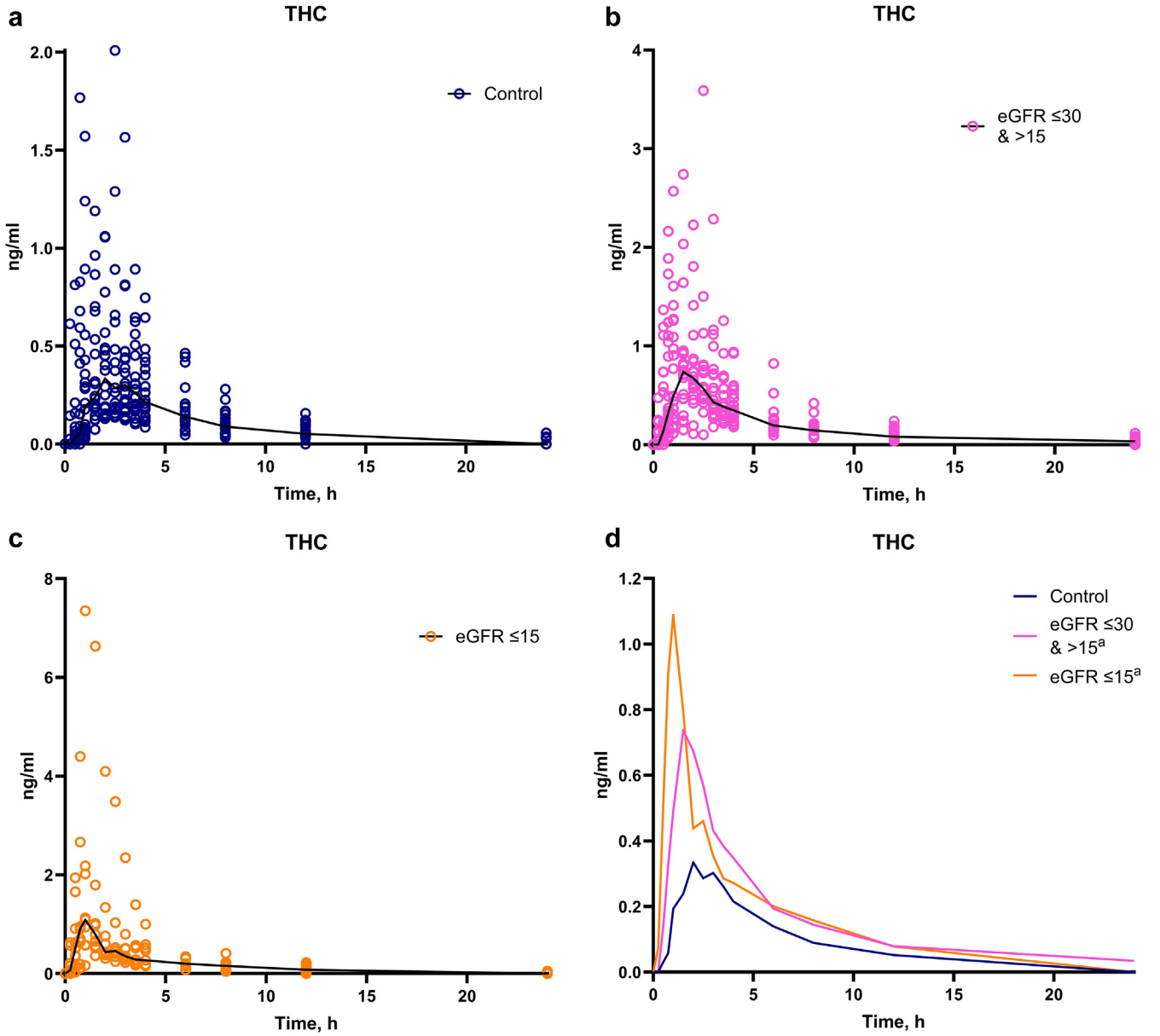

Figure 2. Individual concentrations and median of plasma THC in (a) controls, (b) eGFR ≤ 30 and > 15 ml/min per 1.73 m^2, and (c) eGFR ≤ 15 ml/min per 1.73 m^2, respectively. (d) The 3 median curves of THC concentrations are joined in one graph. eGFR, estimated glomerular filtration rate; THC, Δ^9-tetrahydrocannabinol. Note different scales. [a]significant difference between this group and controls for the area under the curve. Note different scales.

and compared with participants with eGFR ≤ 30 and > 15 (Table 2).

CBD, THC-OH, THC-COOH, and THC-COOH-Glucuronide

In Figure 3, we show plasma concentrations of CBD, THC-OH, THC-COOH, and THC-COOH-glucuronide in the 3 groups. Owing to unmeasurable or very low concentrations of THCA-A and CBDA, pharmacokinetic parameters were not calculated. AUC_{CBD}, $AUC_{THC\text{-}OH}$, and $AUC_{THC\text{-}COOH\text{-}glucuronide}$ were significantly larger for each CKD group compared with the controls (Table 2). $AUC_{THC\text{-}COOH}$ was significantly larger than controls for eGFR ≤ 30 and > 15, but not for eGFR ≤ 15. Likewise, C_{max} was significantly higher for CKD groups compared with controls for CBD, THC-OH, and THC-COOH-glucuronide; and for THC-COOH it was significantly higher for eGFR ≤ 30 and > 15, but not for eGFR ≤ 15. There was a tendency toward a shorter T_{max} for the CKD groups compared with controls; however, it was only significant between controls and eGFR ≤ 15 for CBD and THC-OH. For THC-OH, the difference in T_{max} was significant between the 2 CKD groups (Table 2).

Correlation Between Total Drug Exposure AUC and Renal Parameters

All renal parameters correlated significantly with AUC_{THC} with R^2 values between 0.25 and 0.28

Table 2. Pharmacokinetic parameters

Parameter	Control (n = 20)	eGFR ≤ 30 & > 15 (n = 20)	eGFR ≤ 15 (n = 9)	P value
THC				
AUC, h × ng/ml	2.76 (1.77–3.48) [0.91–5.48]	4.16 (3.35–5.28) [1.97–12.15][a]	4.31 (3.16–5.42) [1.56–18.09][a]	0.004
C_{max}, ng/ml	0.62 (0.37–0.98) [0.18–2.01]	0.94 (0.73–1.45) [0.36–3.59][a]	1.09 (0.70–2.02) [0.65–7.35][a]	0.014
T_{max}, h	1.75 (1.00–2.50) [0.50–6.00]	1.50 (1.00–2.00) [0.75–4.00][b]	1.00 (0.75–1.00) [0.75–1.50][a,b]	0.041
CBD				
AUC, h × ng/ml	1.25 (0.49–1.81) [0.25–4.63]	2.75 (2.49–3.66) [1.57–7.68][a]	3.56 (2.22–4.66) [1.41–11.26][a]	0.000
C_{max}, ng/ml	0.18 (0.12–0.45) [0.06–1.23]	0.68 (0.57–0.87) [0.16–2.25][a]	0.86 (0.47–1.33) [0.29–4.68][a]	0.000
T_{max}, h	2.00 (0.88–2.75) [0.50–6.00]	1.50 (1.00–2.00) [0.75–3.50]	1.00 (0.75–1.00) [0.50–1.50][a]	0.017
THC-OH				
AUC, h × ng/ml	4.92 (2.87–6.98) [1.20–14.05]	18.56 (14.57–23.21) [7.39–45.32][a]	17.99 (16.06–35.66) [10.05–55.16][a]	0.000
C_{max}, ng/ml	0.91 (0.73–1.29) [0.28–2.59]	3.03 (2.11–3.93) [1.07–8.55][a]	2.92 (2.67–5.70) [1.68–10.06][a]	0.000
T_{max}, h	3.00 (2.00–3.50) [0.50–6.00]	2.50 (2.00–2.50) [0.75–4.00][b]	1.50 (1.50–1.50) [1.00–2.00][a,b]	0.002
THC-COOH				
AUC, h × ng/ml	84.60 (68.71–131.18) [3.92–198.41]	149.08 (105.12–190.31) [35.24–234.70][a]	125.88 (124.28–168.78) [72.11–352.00]	0.019
C_{max}, ng/ml	11.90 (8.09–13.98) [1.06–18.27]	16.02 (11.05–17.92) [4.71–25.16][a]	13.70 (11.52–16.72) [9.52–32.39]	0.020
T_{max}, h	2.75 (2.00–3.50) [1.50–6.00]	2.50 (2.00–2.50) [1.50–3.50]	2.00 (1.50–2.50) [1.50–3.00]	0.066
THC-COOH-glucuronide				
AUC, h × ng/ml	396.03 (254.23–457.88) [63.06–960.14]	710.60 (598.12–1064.37) [239.60–1,833.89][a]	940.78 (716.85–1161.48) [681.81–1,927.41][a]	0.000
C_{max}, ng/ml	32.99 (21.29–38.02) [5.05–67.60]	49.02 (39.75–60.67) [16.16–88.62][a]	58.96 (44.04–69.49) [42.39–106.85][a]	0.000
T_{max}, h	5.00 (3.50–6.00) [2.50–8.00]	6.00 (5.00–6.00) [3.50–8.00]	6.00 (4.00–6.00) [3.50–12.00]	0.181

AUC, area under the curve; CBD, cannabidiol; C_{max},maximum concentration;THC, Δ^9-tetrahydrocannabinol; THC-COOH,11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH,11-hydroxy-Δ^9-tetrahydrocannabinol; T_{max}, time to maximum concentration.
The P values refer to Kruskal-Wallis test.
[a]Significant difference compared with controls.
[b]Significant difference between CKD groups.
Presented as median (interquartile range) [minimum–maximum].

(Table 3). If regression analyses were adjusted for age, BMI, and sex, no significant correlations were found. AUC for CBD and metabolites also correlated significantly with all renal parameters with R^2 values between 0.13 and 0.62 (Table 3) and the correlations remained significant when adjusted for age, BMI, and sex (Table 3).

Excretion in Urine

The total excretion of THC-COOH and THC-COOH-glucuronide in 24-hour urine was significantly lower in patients with CKD compared with controls (Figure 4). THC and CBDA were not detected or below the lower limits of quantification for all urine samples. THC-OH and THCA-A were only above the lower limits of quantification in 1 urine sample each. CBD was quantified in 10 urine samples with no difference between groups.

Side Effects

In Figure 5, we show the mean NRS scores for 10 different symptoms. Feeling intoxicated or high (Figure 5a) and dizziness (Figure 5b) peaked after approximately 1 to 2 hours. NRS scores for nausea and hunger differed significantly between controls and eGFR ≤ 30 and > 15 after 1 hour. After 1.5 hours dizziness differed between each CKD group and controls.

Other adverse events reported in the study were generally mild and self-limiting and included dry mouth ($n < 3$), feeling cold ($n < 3$), increased saliva ($n < 3$), bleeding from peripheral venous catheter ($n < 3$), paresthesia in relation to the mouth ($n < 3$), and feeling unwell or vasovagal reaction in connection to peripheral venous catheter manipulation ($n = 3$).

Vital parameters were stable apart from systolic blood pressure for patients with eGFR ≤ 30 and > 15, which was significantly lower at 2 hours after administration of Sativex compared with baseline.

DISCUSSION

To the best of our knowledge, this study is the first to investigate the pharmacokinetics of THC in CKD. We found that the total exposure to THC, CBD, and most metabolites was higher for participants with CKD compared with controls. Furthermore, the patients with CKD reached higher maximal concentrations, excreted metabolites in urine slower, and reported more dizziness compared with controls.

We found a median AUC_{THC} in controls which corresponds to approximately 80% of the AUC found by Stott *et al.*[35] using the same dose in healthy men. For participants with CKD, the median AUC_{THC} was more than 50% larger compared with controls. In our power calculation, we defined a clinically relevant change in AUC to be 50%, which is in line with the 80% to 125%

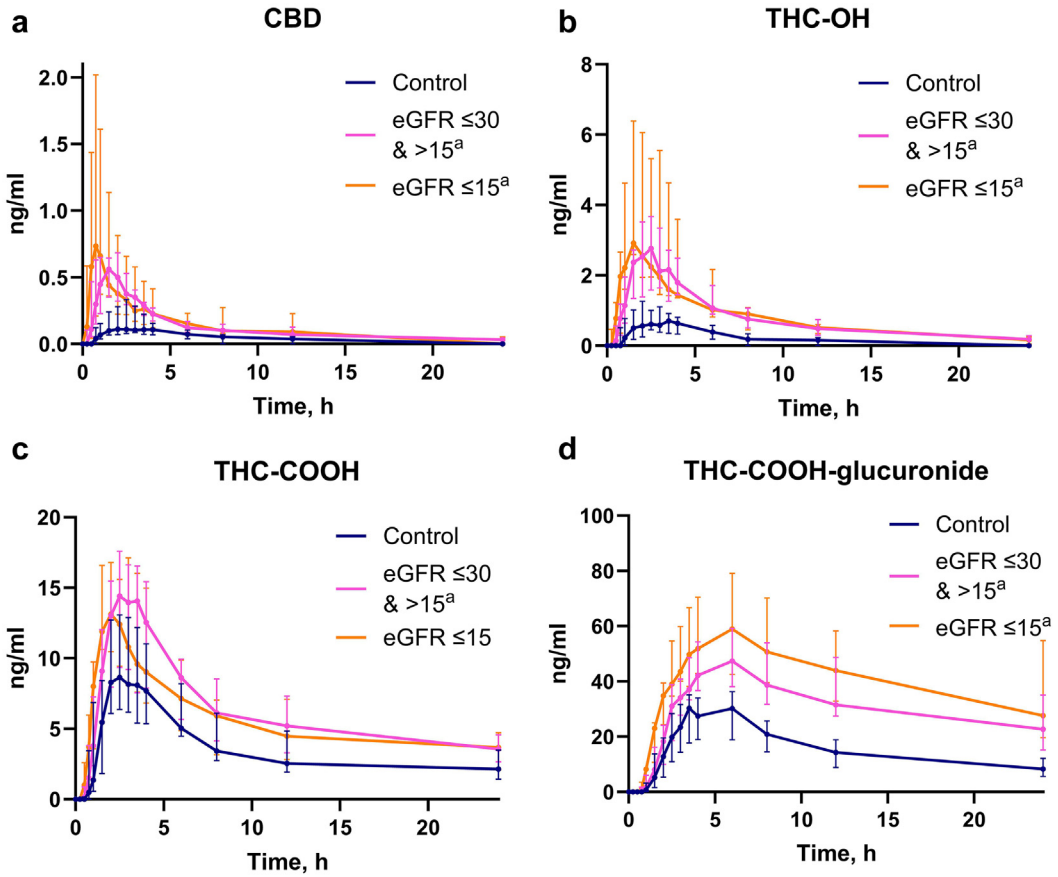

Figure 3. The median plasma concentrations with interquartile ranges for (a) CBD, (b) THC-OH, (c) THC-COOH, and (d) THC-COOH-glucuronide in controls, eGFR ≤ 30 and > 15 ml/min per 1.73 m^2, and eGFR ≤ 15 ml/min per 1.73 m^2, respectively. CBD, cannabidiol; eGFR, estimated glomerular filtration rate; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH, 11-hydroxy-Δ^9-tetrahydrocannabinol. [a]significant difference between this group and controls for the area under the curve. Note different scales.

definition of bioequivalence;[39] thus, our results could be clinically relevant. However, food can increase the AUC for THC and CBD in Sativex approximately 3-and 5-fold, respectively; and the intersubject variability for AUC after 4 sprays of Sativex can be up to 8-fold for THC and 11-fold for CBD.[22,40] In addition, other studies with Sativex found high intersubject variability with resulting high standard deviations for AUC.[41] In our study, the intersubject variability was high in all groups, where AUC varied with up to a factor 18 for AUC_{CBD} in the controls. However, the absolute intersubject variability in AUC appeared higher in CKD groups for both THC and CBD. Median AUC for CBD and metabolites was between 49% and 277% larger in the CKD groups compared with controls, and C_{max} was between 15% and 377% higher for THC, CBD, and metabolites in the CKD groups compared with controls. For controls, we found an apparently smaller AUC, lower C_{max}, and longer T_{max} for THC, CBD, and THC-OH compared with results by Stott *et al.*[35]

We found a significantly lower excretion of THC-COOH and THC-COOH-glucuronide in urine for each CKD group compared with controls, which could contribute to the differences in total exposure. All other measured cannabinoids were not detectable or only detectable in a few samples, which is in line with findings in other studies.[28,42]

Contrary to our results, the pharmacokinetics of a single 200 mg dose of CBD (Epidiolex) has been shown not to be affected by mild, moderate, or severe renal impairment.[28] Several differences between the studies can contribute to the different results. The study with Epidiolex only included 8 participants in each group and matched to controls by age and BMI. They assessed renal function by the Cockcroft-Gault equation, where overestimation of GFR and the included weight measurement are concerns.[2,43–45] In addition, baseline data indicates that most participants had CKD stage 4. We did not match age and BMI, and the uneven distribution in the groups may have influenced our results. We found significant correlations between renal parameters and total exposure for THC, CBD, and metabolites; and if adjusted for age, BMI, and sex, the correlation remained significant for all measured substances, except THC. The renal parameters could explain

Table 3. Regression statistics between renal parameters and log transformed AUC for THC, CBD and metabolites

Parameters	Coefficient (standard error)	*P* value	R^2	$Coefficient_{adjusted}$ ($standard\ error_{adjusted}$)	$P\ value_{adjusted}$	$R^2_{adjusted}$
AUC_{THC}						
$eGFR_{creatinine}$	−0.0067 (0.0017)	0.000	0.25	−0.0031 (0.0025)	0.217	0.32
$eGFR_{cystatin\ C}$	−0.0077 (0.0018)	0.000	0.28	−0.0042 (0.0028)	0.148	0.33
$eGFR_{creatinine\text{-}cystatin\ C}$	−0.0072 (0.0018)	0.000	0.27	−.0037 (0.0027)	0.179	0.33
Absolute $eGFR_{creatinine}$	−0.0057 (0.0014)	0.000	0.26	−0.0028 (0.0021)	0.174	0.33
AUC_{CBD}						
$eGFR_{creatinine}$	−0.013 (0.0020)	0.000	0.48	−0.0089 (0.0030)	0.005	0.53
$eGFR_{cystatin\ C}$	−0.015 (0.0022)	0.000	0.50	−0.010 (0.0034)	0.004	0.54
$eGFR_{creatinine\text{-}cystatin\ C}$	−0.014 (0.0021)	0.000	0.49	−0.0098 (0.0032)	0.004	0.54
Absolute $eGFR_{creatinine}$	−0.011 (0.0017)	0.000	0.49	−0.0077 (0.0025)	0.003	0.54
$AUC_{THC\text{-}OH}$						
$eGFR_{creatinine}$	−0.016 (0.0020)	0.000	0.58	−0.018 (0.0029)	0.000	0.62
$eGFR_{cystatin\ C}$	−0.018 (0.0021)	0.000	0.60	−0.022 (0.0032)	0.000	0.65
$eGFR_{creatinine\text{-}cystatin\ C}$	−0.017 (0.0020)	0.000	0.60	−0.021 (0.0030)	0.000	0.64
Absolute $eGFR_{creatinine}$	−0.014 (0.0016)	0.000	0.62	−0.015 (0.0024)	0.000	0.63
$AUC_{THC\text{-}COOH}$						
$eGFR_{creatinine}$	−0.0058 (0.0022)	0.010	0.13	−0.0094 (0.0030)	0.003	0.32
$eGFR_{cystatin\ C}$	−0.0063 (0.0024)	0.011	0.13	−0.011 (0.0034)	0.002	0.33
$eGFR_{creatinine\text{-}cystatin\ C}$	−0.0061 (0.0023)	0.009	0.13	−0.011 (0.0032)	0.002	0.33
Absolute $eGFR_{creatinine}$	−0.0054 (0.0018)	0.004	0.16	−0.0079 (0.0025)	0.002	0.32
$AUC_{THC\text{-}COOH\text{-}glucuronide}$						
$eGFR_{creatinine}$	−0.011 (0.0017)	0.000	0.44	−0.010 (0.0025)	0.000	0.51
$eGFR_{cystatin\ C}$	−0.012 (0.0019)	0.000	0.45	−0.012 (0.0028)	0.000	0.53
$eGFR_{creatinine\text{-}cystatin\ C}$	−0.011 (0.0018)	0.000	0.45	−0.011 (0.0027)	0.000	0.53
Absolute $eGFR_{creatinine}$	−0.0091 (0.0014)	0.000	0.46	−0.0083 (0.0021)	0.000	0.51

AUC, area under the curve; BMI, body mass index; CBD, cannabidiol; eGFR, estimated glomerular filtration rate; THC, Δ^9-tetrahydrocannabinol; THC-COOH,11-nor-9-carboxy-Δ^9-tetrahydrocannabinol; THC-OH,11-hydroxy-Δ^9-tetrahydrocannabinol.
Values adjusted for age, BMI, and sex.

between 13% and 62% of the variance in the total exposure without adjustments for age, BMI, and sex. Absolute eGFR or eGFR based on cystatin C tended to correlate best with total exposure; however, the differences in correlations between the different renal parameters were not appreciable (Table 3).

In our study, Sativex was well-tolerated in all groups with generally mild and self-limiting side effects. The mean NRS scores for feeling intoxicated or high and dizziness correlated visually well to plasma concentrations of THC, CBD, and THC-OH. Thus, the tendency for patients with CKD to have higher scores for dizziness and feeling intoxicated or high may be concentration dependent. Alternatively, it could be due to a higher sensitivity or placebo effect in patients with CKD. Hunger was influenced by fasting conditions, and sleepiness by a conjunction of other circumstances, which makes a correlation to plasma concentrations difficult to visualize. For all other symptoms, mean NRS scores were low. Given the relatively high THC dose in treatment-naive patients, the low CBD dose, and the side effect profiles of THC and CBD, the side effects are most likely because of THC or its active metabolites rather than CBD.[22,23]

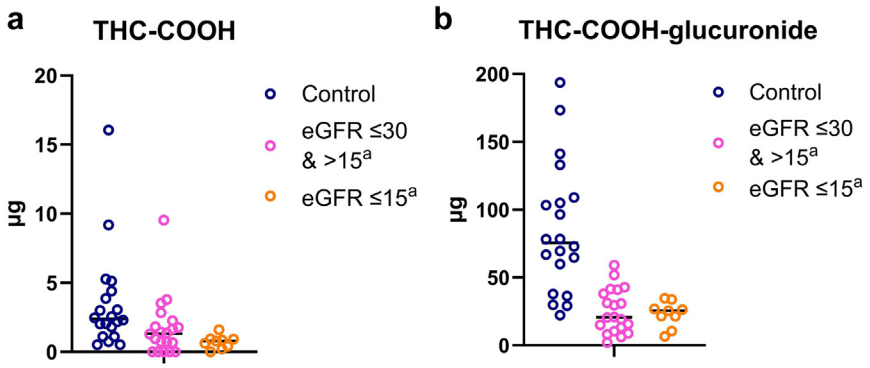

Figure 4. Individual values and medians of total excretion of (a) THC-COOH and (b) THC-COOH-glucuronide in 24-h urine in controls, eGFR ≤ 30 and > 15 ml/min per 1.73 m^2, and eGFR ≤ 15 ml/min per 1.73 m^2, respectively. eGFR, estimated glomerular filtration rate; THC-COOH, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol. [a]significant difference compared with controls. Note different scales.

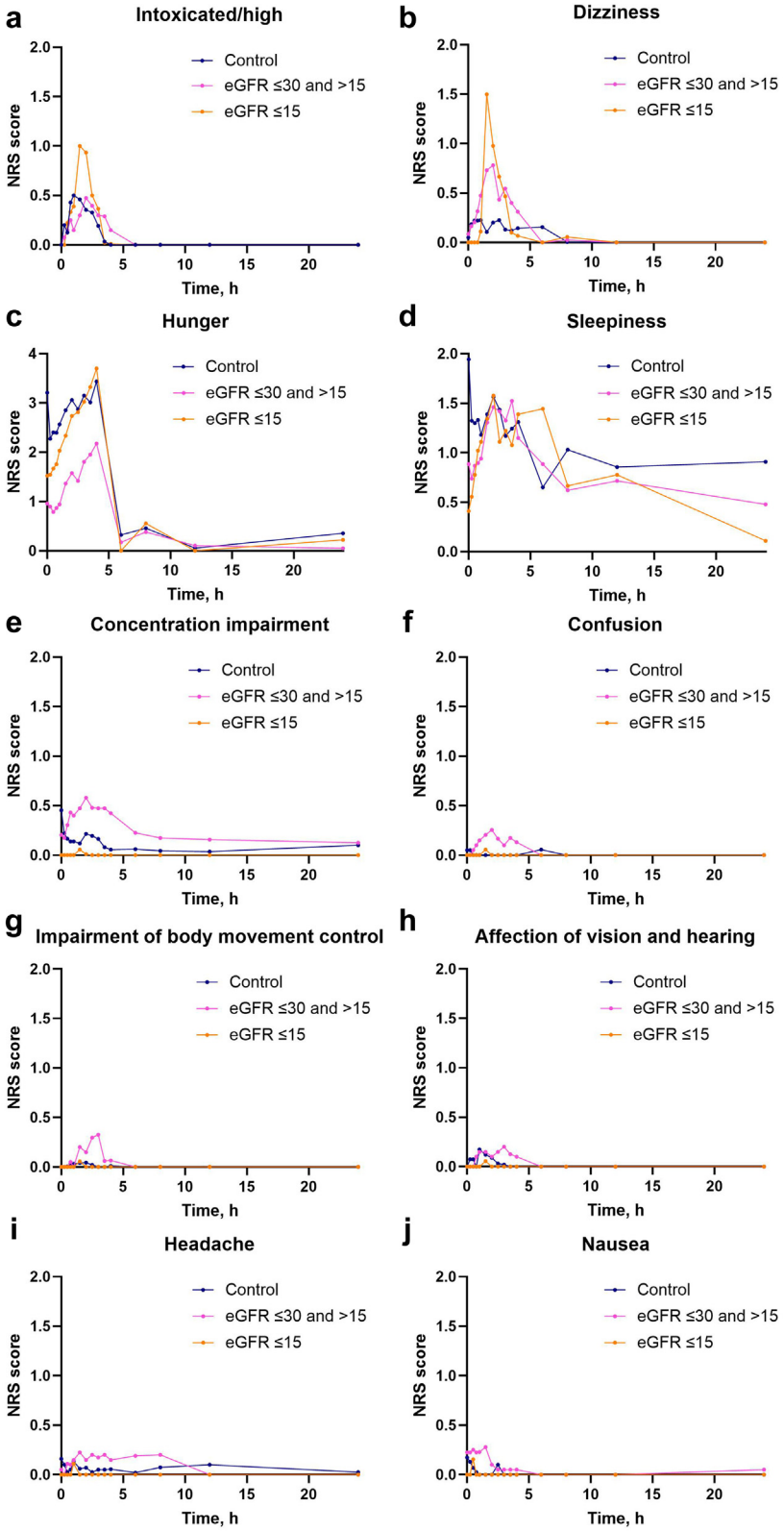

Figure 5. Mean NRS scores for 10 common side effects for controls, eGFR ≤ 30 and > 15 ml/min per 1.73 m^2, and eGFR ≤ 15 ml/min per 1.73 m^2. Note that hunger has a different scale. eGFR, estimated glomerular filtration rate; NRS, Numeric rating scale.

THC interacts with the cannabinoid receptors, known as cannabinoid receptors 1 and 2, and the pharmacodynamics influencing mood, perception, cognition, and psychomotor function are well-known.[18,46] CBD has a low affinity to cannabinoid receptors 1 and 2, and is known to exhibit effect through several other mechanisms such as serotonin receptors (i.e., $5HT_{1A}$), ion channels (i.e., TRPV1), and dopamine

receptors (i.e., D2), and to influence the endocannabinoid system through inhibition of degradation of endocannabinoids.[18,47] The cannabinoid receptors are distributed throughout the body, wherefore the endocannabinoid system may be involved in many physiological processes.[48] Emerging evidence suggests that the endocannabinoid system plays a role in kidney inflammation, fibrosis, and albuminuria, and thereby progression of CKD.[10,49] Currently, a clinical phase 2 study is investigating a peripheral cannabinoid receptor 1 inverse agonist for treatment of diabetic kidney disease.[50] Whether or how cannabis use can influence the risk of acute kidney injury and progression of CKD remains unclear.[51-53]

The pharmacokinetics of hepatically metabolized drugs can be altered in patients with CKD,[25,26] which agrees with our results. These alterations can be explained by several physiological changes in CKD, which include changes in pH, intestinal barrier, activity of CYP-enzymes and drug transporters, protein binding, and volume of distribution (Vd).[25,26] Vd impacts both half-life and C_{max}; an increased Vd may result in lower C_{max}, whereas increased bioavailability would increase C_{max} and may contribute to the higher C_{max} in participants with CKD.[26] Body composition is critical for Vd, because an increase in adipose tissue would directly increase Vd for cannabinoids, which are lipophilic, whereas an increase in body water may not to the same extent. A shortcoming of BMI is that it does not reflect body composition, and we did not assess hydration status or body composition of the participants. The effect of CKD on the pharmacokinetics of nonrenally excreted drugs are complex and difficult to predict.[54]

This study adds valuable knowledge to the pharmacokinetics of THC, CBD, and metabolites in CKD. However, limitations include the single dose design with a low dose, the time limit of 24 hours, where metabolites are still measurable, the fact that only a small fraction of metabolites were measured, and that we only measured the total concentration and not the free concentration of the different cannabinoids. Furthermore, matching of controls and patients with CKD on age and BMI would have been an advantage, and the regression analyses should be interpreted with caution because data were skewed and assumptions not fully satisfied. More participants in the group with eGFR $\leq$ 15 as planned could have provided more robust data on differences in the pharmacokinetics between CKD stages 4 and 5.

Pharmacokinetic knowledge is a start; nevertheless, good quality studies on efficacy are needed, if THC and/or CBD should be generally accepted treatments of symptoms in CKD.

In conclusion, total exposure of patients with CKD to THC, CBD, and metabolites increased to a possibly clinically relevant extent; however, the intersubject variability was high. In addition, dizziness was more pronounced in patients with CKD compared with controls. This suggests that cannabis should be administered with caution to these patients. Furthermore, repeated dosing and the impact of the endocannabinoid system in CKD need further investigation.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The study data are personal sensitive data and therefore cannot be made publicly available because of restrictions imposed by Danish data protection legislation, including the General Data Protection Regulation and the Danish Data Protection Act. Selected data can be available from the corresponding author upon reasonable request after completion of a data sharing agreement, approval from the Danish Data Protection Agency, and the Danish Research Ethics Committees, Central Region Denmark, and if necessary, renewed participant consent in compliance with applicable legal and ethical standards.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Inclusion criteria.

Exclusion criteria.

Questions in the numeric rating scale questionnaire.
CONSORT Checklist.

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