



SYNTHETIC CANNABINOID BONZAI RELATED CREATINE KINASE ENZYME ELEVATION: A TURKISH CENTER STUDY

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SUMMARY – Synthetic cannabinoid (locally named ‘Bonzai’ in Turkey) use is increasing world-wide (especially among people with low income). One of its harmful adverse effects is an increase in serum levels of muscle enzymes (i.e., creatine kinase [CK]). The aim of this study was to determine the prevalence of Bonzai use in patients admitted with elevated CK levels and to compare the 1-month survival status of Bonzai users with that of non-Bonzai users. This retrospective study was conducted on a total of 468 patients, median (min-max) age 48±22 (18-93) years. It was found that 10.68% (n=50) of the patients presenting with elevated CK levels were using Bonzai (group 1), while the remaining 418 (89.32%) patients were non-Bonzai users (group 2). Median age was higher in group 2 as compared with group 1 (p=0.001). In group 1, the predominance of male (M) over female (F) patients was interestingly high, yielding a F:M ratio of 1/49 ($\chi^2=110.03$, p<0.001). The prevalence of Bonzai use among patients admitted to our center with elevated CK levels was 10.68%. The Bonzai group patients were younger and mostly males, and none of them died at 1 month of admission. These findings may help in the management of such clinical conditions and could be a pathfinder for further studies in this field.

Key words: *Addictive substances; Bonzai; Creatine kinase; Synthetic cannabinoids*

Introduction

Synthetic cannabinoids are widely used (as cheap) addictive substances. In western countries, they have various names in street language (such as spice, fake weed, etc.). John Huffman, a Harvard University chemist, was the creator of the first synthetic cannabinoid ‘JWH-018’ in the early 1990s¹. The European Monitoring Centre of Drugs and Drug Addiction (EMCDDA) has identified 102 varieties of this syn-

thetic addictive substance. In Turkey, they are named Bonzai. The chemical name for Bonzai is (1-pentyl-1H-indol-3-yl)-1-naphthalenyl-methanone; the accurate concentration of the active substance found in the under-the-counter products is not known¹⁻³. Bonzai use is associated with many health problems and/or complications³⁻⁶. One of these medical conditions related to the use of Bonzai and other addictive drugs is withdrawal-related rhabdomyolysis and/or elevations in muscle enzymes (such as creatine kinase, CK). The rate of this complication related to synthetic cannabinoid use is around 0.1%⁴. On the other hand, many other conditions may also cause elevated CK levels and CK elevation is a somewhat frequent condition encountered in daily practice³. Therefore, we aimed to

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determine the prevalence of Bonzai use in patients with elevated CK levels admitted to our center during the past year. A secondary aim of this study was to compare the 1-month survival status between Bonzai users and non-Bonzai users.

Material and Methods

This retrospective study was approved by Bakirkoy Dr. Sadi Konuk Training and Research Hospital Ethics Committee. Hereafter, this hospital or center will be abbreviated as Bakirkoy Hospital. The study is reported in accordance with the RECORD Guidelines from the Equator Network⁷.

All patients (≥ 18 years old) with elevated CK levels admitted to Bakirkoy Hospital between January 1, 2019 and December 31, 2019 were assessed for inclusion in the study. All patients with complete hospital records and 1-month survival data were included in the study. To improve consistency, all data were collected by a single researcher who had not been responsible for medical care of any of these patients. Patient data were further reviewed by a commission consisted of BE, MH, and DY.

These patients were grouped by another commission (OP, HD, and HY) according to the presence of definite Bonzai intake history as follows: group 1, patients using Bonzai; and group 2, patients not using Bonzai.

Data on patient age, gender, laboratory test results on admission, and 1-month survival status were collected from hospital records. Death reports were confirmed from the official death reporting system of the Turkish Ministry of Health. Data on a total of 472 patients were reviewed. Records on one male patient could not be fully retrieved (due to being a forensic case). Records on another male patient were not complete. One female patient was excluded because of the use of heroin (not Bonzai). Lastly, information on the 1-month survival status of a female patient (who was not a Turkish citizen) could not be found. Therefore, final analysis was conducted using data on 468 patients.

Statistical analysis

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 statistical software (Utah, USA). Description of data was ex-

pressed by the mean, standard deviation (SD), median (minimum–maximum) and interquartile range (25%–75%), as appropriate. The normality of distribution of variables was checked with the Shapiro Wilks test. T-test for independent samples was used for comparison of variables with normal distribution, and Mann-Whitney U test for comparison of variables with non-normal distribution. Spearman's test was used for evaluation of the correlation between quantitative variables. A p-value of less than 0.05 was accepted as statistically significant.

Results

The mean \pm SD (median [min-max]) CK level of the 468 patients was 5671.66 ± 12499.93 (2207.5 [1000-99547]) mg/dL. Mean (SD) age was 49.88 ± 22 (48 [18-93]) years. The female/male (F/M) ratio of all patients was 114/354. Of the 468 patients, 50 (10.68%) were in group 1 (Bonzai users). In this group, the female to male ratio was in favor of males (F/M=1/49; $\chi^2=110.03$, $p<0.001$). Although age, serum K^{+1} and C-reactive protein (CRP) levels were significantly higher in group 2 (non-Bonzai users) ($p=0.001$, $p=0.012$, and $p=0.029$, respectively), serum levels of glucose, CK, aspartate aminotransferase (AST) and albumin were higher in group 1 ($p=0.001$ all). Serum creatinine, alanine aminotransferase (ALT) and hemoglobin (Hgb) levels showed no significant difference between the two groups ($p>0.05$ all). White blood cell (WBC) and platelet (PLT) counts were both significantly higher in group 1 ($p=0.001$ both). The WBC/PLT ratio was significantly higher in group 2 ($p=0.001$) (Table 1). Between-group difference of these parameters according to gender could not be analyzed in female subjects (there was only one female patient in group 1). So, this comparison was only done in male patients. Results similar to those recorded in both genders were obtained for only male subjects on all study parameters except for CRP (Table 2). Serum CRP levels did not differ between male patients from the two groups ($p>0.05$).

Regarding the 1-month survival status, 54 (11.54%) of 468 patients died during this period. Surprisingly, none of these deceased patients was Bonzai user. Results of Spearman's correlation analysis (correlation coefficients [CC] and p values) of these study parameters are shown in Table 3. All study parameters and

Table 1. Comparison of study parameters in two study groups

	Bonzai (n=50)	Non-Bonzai (n=414)	a _p
Age (years); mean+SD	31.36±10.37	52.12±21.91	0.001**
CK (U/L); median (IQR)	5026 (2442.8-10333.3)	2046.5 (1295.8-3919.8)	b0.001**
Glucose (mg/dL); mean+SD	107.16±25.2	126.22±66.26	0.001**
Creatinine (mg/dL); median (IQR)	0.98 (0.8-1.5)	1.05 (0.8-2.4)	^b NS
Na ⁺ (meq/L); mean+SD	138.9±6.19	137.49±7.35	NS
K ⁺ (meq/L); mean+SD	4.06±0.85	4.39±0.85	0.012*
AST (IU/L); median (IQR)	100 (57.8-163)	67 (43-116.8)	b0.001**
ALT (IU/L); median (IQR)	44.5 (27.5-68.8)	38 (23-68)	^b NS
Albumin (mg/dL); mean+SD	4.46±0.74	3.8±0.82	0.001**
CRP (mg/dL); median (IQR)	1.78 (0.6-3)	2.76 (0.4-13.2)	b0.029*
Hgb (g/dL); median (IQR)	4.71 (3.2-8.1)	6.17 (4.3-8.4)	^b NS
WBC (10 ³ /mm ³); mean+SD	15.37±1.95	12.69±2.8	0.001**
PLT (10 ³ /mm ³); median(IQR)	14.9 (11.6-18.7)	9.16 (7-12.2)	^b 0.001**
WBC/PLT ratio; median (IQR)	1.03 (0.8-1.3)	1.39 (0.9-2)	b0.001**

Bold = normally distributed parameters; CK = creatine kinase; Na = sodium; K = potassium; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CRP = C-reactive protein; Hgb = hemoglobin; WBC = white blood count; PLT = platelet count; NS = nonsignificant; SD = standard deviation; IQR = interquartile range (25%-75% percentile); ^aindependent samples t-test; ^bMann Whitney U test; *p<0.05; **p<0.01

Table 2. Comparison of study parameters between males from two study groups

Male (N=354)	Bonzai (n=49)	Non-Bonzai (n=305)	a _p
Age (years); mean+SD	31.57±10.36	48.88±21.55	0.001**
CK (U/L); median (IQR)	4813 (2428.5-9984.5)	2183.5 (1299.3-4211.5)	b0.001*
Glucose (mg/dL); mean+SD	107.2±25.46	118±52.06	0.025*
Creatinine (mg/dL); Median (IQR)	0.98 (0.8-1.6)	1.06 (0.9-2.3)	^b NS
Na ⁺ (meq/L); mean+SD	138.84±6.24	138.3±6.47	NS
K ⁺ (meq/L); mean+SD	4.05±0.86	4.36±0.74	0.010*
AST (IU/L); median (IQR)	93 (57.5-163)	67 (43-117.5)	b0.004**
ALT (IU/L); median (IQR)	40 (27-70.5)	40.5 (24-72.3)	^b NS
Albumin (mg/dL); mean+SD	4.49±0.72	3.85±0.86	0.001**
CRP (mg/dL); median (IQR)	1.79 (0.6-3)	2.33 (0.3-13.4)	^b NS
Hgb (g/dL); median (IQR)	4.71 (3.2-8.1)	5.86 (4-8.7)	^b NS
WBC (10 ³ /mm ³); mean+SD	15.41±1.95	13.12±2.8	0.001**
PLT (10 ³ /mm ³); median (IQR)	14.88 (11.6-18.9)	9.06 (7.1-11.9)	b0.001**
WBC/PLT ratio; median (IQR)	1.04 (0.8-1.3)	1.45 (1-2)	b0.001**

Bold = normally distributed parameters; CK = creatine kinase; AST = aspartate aminotransferase; Na = sodium; K = potassium; ALT = alanine aminotransferase; CRP = C-reactive protein; Hgb = hemoglobin; WBC = white blood count; PLT = platelet count; NS = nonsignificant; SD = standard deviation; IQR = interquartile range (25%-75% percentile); ^aindependent samples t-test; ^bMann Whitney U test; *p<0.05; **p<0.01

Table 3. Correlation of analysis results

	Age	Gender (F)	Bonzai+	CK	K+1	AST	Albumin	CRP	WBC	PLT	WBC/PLT	Mortality
Age	CC	0.268	-0.295	0.291	0.039	-	-0.539	0.557	-0.551	-0.551	-0.268	-0.317
	P	<0.001	<0.001	<0.001	NS	0.096	<0.001	0.001**	<0.001	0.001**	<0.001	<0.001
Gender (F)	CC	-	-0.180	-0.114	0.011	-0.47	-0.184	0.065	-0.309	-0.045	-0.066	-0.061
	P	-	<0.001	0.014	NS	NS	<0.001	NS	<0.001	NS	NS	NS
Bonzai+	CC	-0.180	-	0.250	-0.164	0.144	0.238	-0.110	0.283	0.272	-0.58	-0.122
	P	<0.001	-	<0.001	<0.001	0.002	<0.001	0.023	<0.001	<0.001	<0.001	0.008
CK	CC	-0.291	0.250	-	-0.092	-	0.119	-0.073	0.207	0.078	0.017	0.082
	P	<0.001	<0.001	-	NS	0.094	0.014	NS	<0.001	NS	NS	NS
K+1	CC	0.039	-0.164	-0.092	-	-	0.032	-0.090	-0.033	-0.094	0.013	-0.115
	P	NS	<0.001	NS	-	0.094	NS	NS	NS	NS	NS	0.016
AST	CC	-0.096	0.144	-0.094	-0.094	-	-0.091	0.079	0.074	0.043	0.013	-0.115
	P	0.038	0.002	NS	0.049	-	NS	NS	NS	NS	NS	0.016
Albumin	CC	-0.539	0.238	0.119	0.032	-	-	-0.654	0.589	-0.152	0.376	0.315
	P	<0.001	<0.001	<0.001	NS	0.091	-	<0.001	<0.001	0.002	0.001**	<0.001
CRP	CC	0.557	-0.110	-0.073	-0.090	0.079	-0.654	-	-0.457	0.263	-0.416	-0.327
	P	<0.001	<0.001	NS	NS	NS	<0.001	-	<0.0001	0.001**	<0.001	<0.001
WBC	CC	-0.551	0.283	0.207	-0.033	0.074	0.589	-0.457	-	0.020	0.378	0.292
	P	<0.001	<0.001	<0.001	NS	NS	<0.001	<0.001	-	NS	<0.001	<0.001
PLT	CC	-0.551	0.272	0.078	-0.094	0.043	-0.152	0.020	0.020	-	-0.890	-0.128
	P	<0.001	<0.001	NS	NS	NS	NS	<0.001	-	-	<0.001	0.008
WBC/PLT ratio	CC	-0.268	-0.58	0.017	0.069	0.013	0.376	-0.416	0.378	-0.890	-	0.220
	P	<0.001	<0.001	NS	NS	NS	<0.001	<0.001	<0.001	<0.001	-	<0.001
Mortality	CC	-0.317	-0.122	0.082	-0.115	-0.091	0.315	-0.327	0.292	-0.128	0.220	-
	P	<0.001	0.008	NS	0.016	NS	0.001	<0.001	<0.001	0.008	<0.001	-

Bold = normally distributed parameters; F = female; CC = Spearman's correlation coefficient; CK = creatine kinase; K = potassium; AST = aspartate aminotransferase; CRP = C-reactive protein; WBC = white blood count; PLT = platelet count; NS = nonsignificant; *p<0.05; **p<0.01

1-month mortality showed a significant (but weak) correlation with Bonzai use.

Discussion

Synthetic cannabinoid addiction is a major problem in the world and in Turkey as well. Besides the psychological and emotional effects of these compounds, their other adverse health effects are not well known. Another important issue is that the exact content and/or concentration of these substances is not known (therefore, their effects and/or adverse effects cannot be estimated and they change from one user to another)¹⁻⁴. Although there are many case reports of rhabdomyolysis and CK elevation associated with synthetic cannabinoid use, clinical (case-control) studies in this field are scarce^{3,4,8}. The rate of CK elevation that might be related to synthetic cannabinoid use in our center was 10.68% (of all elevated CK cases). This rate is not negligible and needs great attention. Given the constantly changing chemical composition of these designer drugs and the inability to determine their blood levels, we could not assess if this adverse effect was due to the use or withdrawal of the substance. As declared and confirmed by the patients and their relatives, group 1 included patients addicted to Bonzai. Besides this declaration, all group 1 patients were referred to the Turkish Ministry of Health Alcohol and Substance Use Disorder Treatment Center (named AMATEM) for further treatment and follow-up upon request from the patients and/or their relatives. One of the other features of the Bonzai users was that 98% of them were male (CC=-0.180, $p<0.001$). This gender difference in Bonzai use is most probably a community and/or region related phenomenon⁹. Also, the age of Bonzai user patients was significantly lower than that of the patients not using Bonzai (31.36 ± 10.37 vs. 52.12 ± 21.91 years, $p=0.001$); the rate of Bonzai use increased with decreasing age (CC=-0.295, $p<0.001$). Younger age and male gender may be a clue for investigating Bonzai use as a possible etiology of CK elevation (at least in our country and neighboring communities). The commonly used parameters of WBC and PLT counts were also evaluated in this study. Surprisingly, WBC and PLT counts were found to be significantly higher in patients using Bonzai, but the WBC/PLT ratio was higher in patients not using Bonzai

(Tables 1 and 2). Large scale studies are needed to explain these issues.

Another important finding of this study was that none of the Bonzai group patients died at the end of the first month of admission. Further follow-up is needed to assess long-term mortality status of these patients.

Limitations

The main limitation of this study was its retrospective nature. Another limitation was that it presented only a single center experience. Istanbul is a metropolis and the most crowded city in Turkey. It is also one of the most crowded cities in the world. Bakirkoy Hospital, the institution where the study was conducted, is one of the biggest referral teaching hospitals in this city. The last limitation of this study was the inability to determine blood levels of the culprit substance⁸, compromising the causality of this adverse event¹⁰. Even in the well-known topics (such as contrast-induced acute kidney injury, CI-AKI), the direct cause or blame is not so easy to identify. The last consensus report from the American College of Radiology and the National Kidney Foundation states that most of the reported cases of CI-AKI are most probably not CI-AKI but rather cases of contrast-associated AKI¹¹. Still, in daily practice, we consider this risk of AKI in high-risk populations. The observed CK elevations in our group 1 patients may better be interpreted as Bonzai-associated (rather than Bonzai-induced) events. Despite these limitations, the findings of this study could be a pathfinder for further detailed studies in this field.

Conclusion

Our study results showed the rate of Bonzai use in inpatients with elevated CK levels in our center to be 10.68%. Patients with elevated CK levels related with Bonzai use were younger and mostly males. Another point to mention is that there was no mortality at one month of admission in the Bonzai group. However, further detailed studies are needed in this field, while the findings described may help the health professionals dealing with such patient groups.

Data availability

Data are available to researchers (for research purpose only) on request by contacting the corresponding author.

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Sažetak

PORAST ENZIMA KREATIN KINAZE POVEZAN SA SINTETSKIM KANABINOIDOM BONZAI: ISTRAŽIVANJE CENTRA U TURSKOJ

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Uporaba sintetskog kanabinoida (u Turskoj nazvan "bonzai") povećava se diljem svijeta (osobito među osobama nižih primanja). Jedan od štetnih učinaka ove tvari je porast razina mišićnih enzima (tj. kreatin kinaze, CK) u serumu. Cilj istraživanja bio je utvrditi učestalost uporabe tvari bonzai kod bolesnika primljenih s povišenim razinama CK i usporediti jednomjesečno preživljenje korisnika tvari bonzai i bolesnika koji ne uzimaju bonzai. Ovo retrospektivno istraživanje obuhvatilo je ukupno 468 bolesnika, medijan (minimum-maksimum) dobi 48±22 (18-93) godine. Utvrđeno je da 10,68% (n=50) bolesnika primljenih s povišenim razinama CK uzima bonzai (1. skupina), dok preostalih 418 (89,32%) bolesnika nije uzimalo bonzai (2. skupina). Medijan dobi bio je viši u 2. skupini u usporedbi s 1. skupinom (p=0,001). U 1. skupini muški bolesnici (M) uvelike su prevladavali nad bolesnicama (F), s F:M omjerom 1/49 ($\chi^2=110,03$; p<0,001). Učestalost uporabe tvari bonzai među bolesnicima primljenima u naš centar s povišenim razinama CK bila je 10,68%. Bolesnici iz skupine koja je uzimala bonzai bili su mlađi i uglavnom muškarci i nitko od njih nije umro unutar mjesec dana od prijma u bolnicu. Ovi nalazi mogli bi pomoći u liječenju ovakvih kliničkih stanja te uputiti na daljnja istraživanja u ovom području.

Ključne riječi: *Psihoaktivne tvari; Bonzai; Kreatin kinaza; Sintetski kanabinoidi*