Global Journal of
Addiction & Rehabilitation Medicine
ISSN: 2573-2447

Juniper Publishers
key to the Researchers

Research Article
Volume 3 Issue 1 - August 2017
DOI: 10.19080/GJARM.2017.03.555605

Glob J Add & Rehab Med

Effect of Cannabis Abuse and Ezymatic Alterations to Endorse Liver Dysfunctions

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Submission: August 03, 2017; **Published:** August 16, 2017

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Abstract

The present study is carried out to investigate the effect of cannabis abuse on liver functions by applying the liver function test to figure out the occurrence of enzymatic changes of the Cannabis Abusers and control group of Kashmir valley. The sample consisted of 250 (Liver function test) of male respondents; of these 125 were belong to cannabis abusers and 125 belong to control group were taken into consideration. The results of study showed that the two groups significantly differed on all the levels of liver function test (LFT). Cannabis abusers showed higher level of Total Bilirubin, Bilirubin direct, Bilirubin indirect, Aspartate amino transferase, Alinine amino transferase, Alkaline phosphate and Gamma glumutal transfersae and have showed lower levels of the protein total, Albumin, Gloublin and A:G ratio in comparison with control group.

Background: The menace of cannabis abuse has reached its peak in the Kashmir valley and is not only a socially unacceptable reality, but in its entirety is a disease and emerging as a major public health challenge not only in Kashmir region but throughout the globe.

Keywords: *Cannabis abuse;* Bilirubin; SGOT; SGPT; Albumin; Globulin & Gamma glumutal transfersae

Abbreviations: THC: Tetrahydrocannabinol; SMHS: Shri Maharaja Hari Singh High Streets; DDRC: Drug De-addiction and Rehabilitation Centre; PCR: Police Control Room

Introduction

The valley of Kashmir is geographically ideal for growing cannabis plants. It grows naturally on hills as well as plane regions in all the districts of the valley. Cannabis, one of the easy obtainable psycho-active drugs used by Kashmiri youth and is generally familiar by Charas, Tamookh, Aiter and Gardi in native languages. Kashmiri people are motivated and manipulated for its cultivation in their fields by its demand and price value in the international market somehow lack of vision and knowledge among drug peddlers squeezed the valley in hollowness. Cannabis addiction wore and spread among Kashmiri youth furiously that can't control enough so far, which ruin school and college going students across the valley. It has been seen that the students mainly of the adolescence age bunk their classes to extract the cannabis for intoxication .It has became a fashion for them to entertain their selves with its abuse. Researchers analyzed 20% students whether boys or girls from missionary schools are cannabis addicted in the valley. Now a day's it becomes a door step problem for parents to tackle and to protect their children from this alarming circumstance.

According to the data of Government Psychiatric Hospital Srinagar Kashmir India, the total numbers of drug addicts enrolled from January 2008 to May 2017 are 105,513 in which total number of inpatient are 38761 and the total number of outdoor patients are 66752. The psychiatric diagnosis applied on patients with the help of to ICD- classification revealed that the total no. of (F10 alcohol users 7365), (F11 opioid users 5252), (F12 cannabis users 22750), (F13 sedative users 13900), (F14 cocaine users 6513), (F15 stimulants users 10872), (F16 hallucinogens users 4522), (F17 nicotine users 1502), (F18 inhalant users 2044) and (F19 multiple drug users 30793). According to the data of Government Shri Maharaja Hari Singh High Streets Hospital Srinagar Kashmir (SMHS), the total numbers of drug addicts enrolled from January 2007 to May 2017 are 105773 in which total number of inpatient are 41241 and the total number of outdoor patients are 64532.

The psychiatric diagnosis applied on patients with the help of to ICD- classification revealed that the total no. of (F10 alcohol users 19729), (F11 opioid users 14688), (F12 cannabis users 25785), (F13 sedatives users 8712), (F14 cocaine 1630), (F15 stimulants are 1094), (F16 hallucinogens users 743), (F17 nicotine users 966), (F18 inhalant users 1464) and (F19 multiple drug users 30930). According to the data of Drug De-addiction and Rehabilitation Centre Police Control Room Srinagar Kashmir (DDRC, PCR), the total numbers of drug addicts enrolled from February 2014 to June 2017 are 16850 in which total number of inpatient are 1414 and the total number of outdoor patients are 16850. The psychiatric diagnosis applied on patients with the help of to ICD- classification revealed that the total no. of (F10 alcohol users 662), (F11 opioid users 1699), (F12 cannabis users 8245), (F13 sedatives users 1395), (F14 cocaine users 476), (F15 stimulant users 513), (F16 hallucinogen users 469), (F17 nicotine users 118), (F18 inhalant users 491) and (F19 multiple drug users 4226).

According to the data of Drug De-addiction and Rehabilitation Centre District Baramulla Kashmir, the total numbers of drug addicts enrolled from January 2012 to June 2017 are 13406 in which total number of inpatient are 4784 and the total number of outdoor patients are 8622. The psychiatric diagnosis applied on patients with the help of to ICD- classification revealed that the total no. of (F10 alcohol users 1245), (F_{11} opioid users 1252), (F_{12} cannabis users 2524), (F_{13} sedatives users 1056), (F14 cocaine users 120), (F_{15} stimulants users 651), (F_{16} hallucinogens users 374), (F_{17} nicotine users 85), (F_{18} inhalants users 339) and (F_{19} multiple drug users 5760). According to the data of Drug De-addiction and Rehabilitation Centre District Islamabad Kashmir, the total numbers of drug addicts enrolled from 2012 to 2017 are 8332 in which total number of inpatient are 2802 and the total number of outdoor patients are 5450.

The psychiatric diagnosis applied on patients with the help of to ICD- classification revealed that the total no. of (F10 alcohol users 1089), (F_{11} opioid users 967), (F_{12} cannabis users 2087), (F_{13} sedatives users 648), (F_{14} cocaine users 140), (F_{15} stimulants users 324), (F_{16} hallucinogens users 280), (F_{17} nicotine users 90), (F_{18} inhalants users 144) and (F_{19} multiple drug users 2568). Data of concerning drug addiction and rehabilitation centers of the Kashmir valley postulates hypothesis that the cannabis is the first psychoactive drug after cigarette smoking used by youth and the average rate of cannabis intoxication is higher as compared to other drug use. The emerging consequence on physical health problems with cannabis abuse is far away from conscience of Kashmiri people so that the present study tries to estimate the drastic changes in some liver enzymes and figure out the effects of cannabis abuse on health due to enzymatic alteration which deliver the clinical importance twisted by the chronic cannabis abuse among humans.

Literature Review

Cannabis and its constituents have affected certain hepatic enzymes and causing a certain degree of liver dysfunction and liver were the major leakage sources of these enzymes [1]. The exotic effect of delta 9- tetrahydrocannabinol (THC) provoked preserve of certain liver enzymes used to digest the hepatic glycogen [2]. It was found that the activities of ALT and AST of cannabis users were significantly lower than the control group [3]. The natural cannabinoids such as O9-tetrahydrocannabinol (THC) have shown therapeutic potential in treating inflammatory diseases. Intraperitoneal administration of THC reserved hepatitis as shown by significant decrease in liver enzymes and reduced liver tissue injury.

Cannabinoids are possible hepatotoxic substances associated with hepatic morphologic and enzymatic alterations [4]. It also increase the (ALP) activity in both injected rats and human smokers and this will increase with the increase of dose and time but the (ALT) and the (AST) increase at the beginning of consumption then will decrease with time [5]. On the other hand it was seen that SGPT is more susceptible evaluating hepatocelluar damage than SGOT [6]. Ironically, in patients with hepatitis C virus infection, daily cannabis use enlarged fibrosis succession instead of defensive patients against it [7]. It was also seen that in marijuana smokers, the mean GGT activity was 86.6% higher than that of the control group and that of alkaline phosphatase (ALP) was 121.7% higher than that of the non smokers group.

In addition, the total bile acids, which were synthesized from cholesterol in the liver, as well as the acetyl cholinesterase activity, were 39.2% higher and 11.3% lower than those of the corresponding control values, respectively. However the mean nitric oxide level was dramatically increased in sera of marijuana smokers (10.8%), the C-reactive protein level was only 40 % higher in sera of marijuana smokers compared with those of the control group. Also, the mean SGPT activity was 19.4 % and that of bilirubin level was 39.1 % higher in sera of the smoker group than those of the healthy control group [8]. THC suppresses the production and induces the apoptosis of human hepatic myofibroblasts and stellate cells via CB2 receptors [9] and thus may be antifibrotic and hepatoprotective [10].

Cannabis addiction exaggerated the blood chemistry and affect neural functions mediated by these biogenic amines neurotransmission, while serotonin and 5HIAA levels were reduced and serum catecholamine levels were potentiated [11]. Endocannabinoids are lipid mediators of the same cannabinoid (CB) receptors that arbitrate the effects of marijuana. The endocannabinoid system (ECS) consists of CB receptors, endocannabinoids, and the enzymes implicated in their biosynthesis and degradation, and it is present in both

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brain and peripheral tissues, including the liver. The hepatic endocannabinod system is activated in different liver diseases and contributes to the causal pathologies.

In patients with cirrhosis of various etiologies, the activation of vascular and cardiac CB1 receptors by macrophage-derived and platelet-derived endocannabinoids contribute to the vasodilated state and cardiomyopathy, which can be reversed by CB1 obstruction [12]. CB2 receptors are articulated mainly in immune and hematopoietic cells and detected in the liver in certain pathological states [7,9,10,13] Additional CB receptors may subsist but their prospective role in liver biology is unknown. Arachidonoyl ethanolamide also acknowledged as anandamide, was the first such ligand discovered [14] with 2-arachidonoyl glycerol (2-AG) identified 3 years later.

Supplementary endogenous ligand recognized such as arachidonoyl ethanolamide and 2-AG are generated on claim in response to swell in intracellular calcium or metabotropic receptor commencement [15]. Their biosynthesis from membrane phospholipids precursors may proceed along multiple parallel pathways [16,17]. Once released, they stay frequently membrane-associated because of their hydrophobic nature, and they can be taken up by cells via a high-affinity uptake mechanism [18]. This is followed by their enzymatic deprivation. Whereas 2-AG preferentially ruined by monoglyceride lipase [19].

While CB2 receptors are untraceable in the normal liver but are induced in pathological conditions such as nonalcoholic fatty liver disease [1], the embryonic state [20]. Liver fibrosis, [7,9,10] regenerating liver, [21] and hepatocelluar carcinoma. Hepatic endocannabinoid levels are analogous to those in the brain, [22,23]. CB2 receptors, which are usually undetectable in the liver, are significantly expressed in the cirrhotic human liver and are also detectable in nonparenchymal liver cells in the fibrotic mouse liver [7,9]. The literature regarding many of its pharmacological and toxicological effects is unconvincing. This study will help to improvise the greater understanding of cannabis abuse and its penalty on liver functioning among humans and identifying gaps in the current literature.

Aim

The aim of the present study is to see the enzymatic alternation produced by cannabis abuse and to analyze the differences on liver function test (LFT) applied to a sample of 125 Cannabis Abusers and 125 from control group.

Hypothesis

There will be significant differences in Bilirubin total, Bilirubin direct, Bilirubin indirect, Aspartate amino transferase, Alanine amino transferase, Alkaline phosphate, Gamma glutamyl transferase , Albumin ,Globulin, A:G RATIO (albumin-globulin ratio) levels between cannabis abusers and control group of kashmiri youth male.

Methodology

Sample

The sample consisted of 250 (LFT) tests of the male respondents. Of these, 125 were belong to cannabis Abusers remaining 125 were belong to control group. The mean age of the sample was 25.32 years. The Cannabis Abusers were selected from Drug De-addiction and Rehabilitation Center Police Control Room, Srinagar Kashmir, where as Non-abusers were randomly selected from Dahis clinical diagnostic labs Ganderbal Kashmir.

Tool used

Liver function test (LFT) is taken as a tool to analyze the enzymatic alteration produced by cannabis abuse (Table 1) (Figure 1).

Table 1: Depicts the mean SDs and t-values on (LFT) in cannabis abusers and control group of Kashmiri valley.

Liver Function Test Serum	Methods	Biological Reference Range
Bilirubin total Bilirubin direct Bilirubin indirect	Spectrophotometry, Diazo Method	0.30-1.20 0.00-0.20 0.20-1.00
Aspartate Amino Transferase (SGOT) Alanine Amino Transferase (SGPT)	Spectrophotometry, UV With Pyridoxal -5-Phosphate	15 – 37 16 – 63
Alkaline Phosphate	Spectrophotometry, PNP AMP Kinetic	46.0 - 116.0
Gamma Glutamyl Transferase	Spectrophotometry, G- Glutamyl-Carboxy-Nitroanalide	15 – 85
Protein Total	Spectrophotometry, Biuret	6.4 - 82
Albumin Gloublin A: G Ratio	Bromcresol Purple (BCP)	3.4 - 5.0 2.0 - 4.10 1.0 - 2.1

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Liver Function Test	Cannabis	abusers	Control group		
	Mean	SD	Mean	SD	t-value
Total Bilirubin	14.78	3.10	11.1	3.23	3.86**
Bilirubin Direct	9.14	3.98	5.07	2.10	4.32**
Bilirubin Indirect	10.04	4.03	7.83	1.98	2.65**
Aspartate Amino Transferase (SGOT)	29.12	4.55	19.09	3.16	6.69**
Alanine Amino Transferase (SGPT)	38.82	7.31	22.01	4.36	8.89**
Alkaline Phosphate	75.72	19.87	51.6	10.62	7.46**
Gamma Glutamyl Transferase	68.82	11.48	48.78	21.01	5.67**
Protein Total	9.97	0.58	9.97	0.55	3.78**
Albumin	4.54	0.24	2.44	0.04	2.75**
Gloubulin	4.98	0.69	2.03	0.51	3.89**
Albumin/globulin (A:G) Ratio	3.44	1.85	6.71	2.27	2.98**

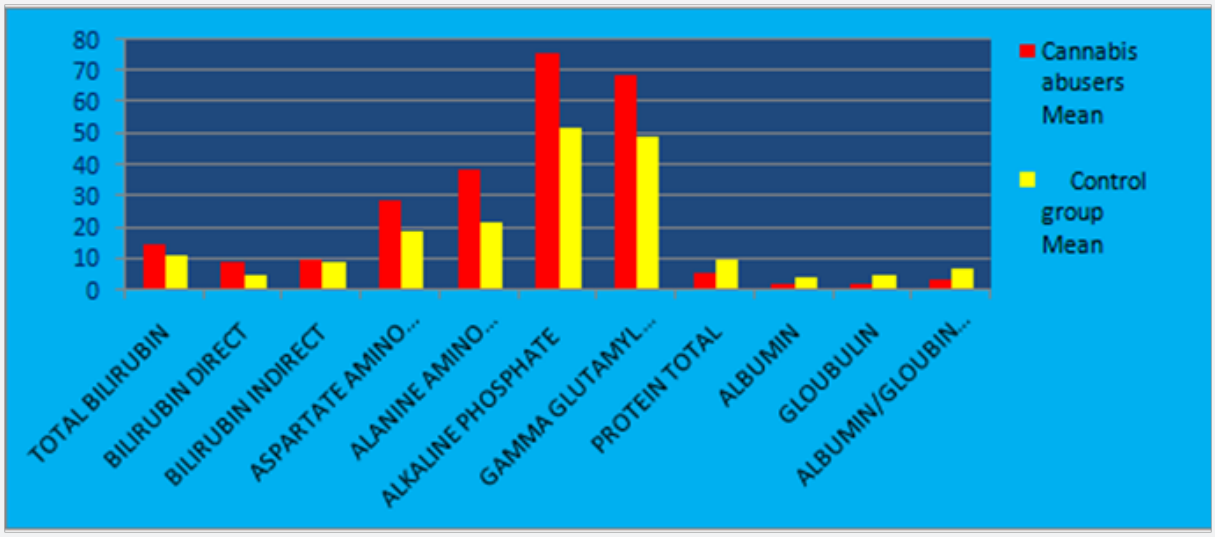

Figure 1: Depicts mean values on (LFT) in cannabis abusers and control group.

Result and Discussion

The t-test was applied to the obtained data to analyze the significance of a difference between the two groups, Cannabis Abusers and control group liver function test (Figure 1 and Table 1). The results showed the values of total Bilirubin, Bilirubin direct, Bilirubin indirect, Aspartate amino transferase, Alinine amino transferase, Alkaline phosphate and Gamma glumutal transfersae higher for the abusers group then those of the control group. Coherently, the level of the protein total, Albumin, Gloublin and A: G ratio is lower for the abusers group then those of the control group. The "t" value on all the levels of (LFT) showed significant difference at (P<0.01).

Cannabis abusers showed higher scores in Total Bilirubin level of the Liver function test (M=14.78) in comparison of control group (M=11.1). In context of Bilirubin Direct level the cannabis abusers showed higher scores (M=9.14) in comparison of control group (M=5.07). In prespective of Bilirubin Indirect level the cannabis abusers showed higher scores (M=10.04) in comparison of control group (M= 7.83). Literature revealed that the Bilirubin is formed by the bustle of biliverdin reductase on biliverdin, a green tetrapyrrolic bile pigment that is also a product of heme catabolism. Bilirubin, when oxidized, reverts to become biliverdin once again and the potent antioxidant activity of bilirubin has led to the supposition that its main physiologic role is as a cellular antioxidant [24-26]. In the absence of liver disease, individuals with high levels of total bilirubin may experience various health benefits exceeding those with lower levels of bilirubin [27]. In other studies it was found that the higher levels of bilirubin in elderly individuals are associated with higher functional independence [28] but somehow the levels of serum bilirubin are inversely related to risk of certain heart diseases [2,29]

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In the present study cannabis abusers showed higher scores in Aspartate amino transferase level (SGOT) (M=29.12) in contrast with control group (M=19.09) and in Alanine amino transferase level (SGPT) cannabis abusers showed higher scores (M=38.82) in relation with control group (M=22.01). A single dose of delta 9-THC succeeded in inhibiting hepatic microsomal enzymes but Serum glutamate oxaloacetate transaminase (SGOT) activity was amplified appreciably in adult male rats exposed to hashish smoke for 50 min, whereas serum glutamate pyruvate transaminase (SGPT) activity was impassive. The enzymes are to be the more insightful determine for evaluating hepatocellular damage and showed severely improved activity in the plasma ALT and AST in rat groups [30-33].

In context of Alkaline phosphate level of liver function test cannabis abusers showed higher scores (M=75.72) in contrast with control group (M=51.6). Cannabis abusers showed higher scores in Gamma glumutal transferase level (M=68.82) in comparison with control group (M=48.78). In addition, the serum gamma glutamyl transpeptidase (GGTP), alanine aminotransferase (AlT), aspartate aminotransferasen (AsT), and alkaline phosphatase (ALP) activities in 40 drug dependent patients. GGTP elevation was observed in 50% of drug estimate changes in some enzymes of clinical importance in rats exposed to cannabinoids and in men addicted to Cannabis smoking. Injection of rats with different doses of petroleum ether extract of Cannabis sativa resulted in a marked change in these plasma enzymes activities.

Alkaline phosphatase (ALP) activity was increased in rats with the increase of dose and time and the difference between the level in the high and the low dose groups was significant during and after the experimental period. Alanine aminotransferase (ALT) activity showed incredible increase after the second dose in the high dose group compared to the control group but returned to a lower level after the last dose, and Aspartate amino transferase (AST) activity revealed also significant elevation after the second dose, but after the last dose the activity decreased significantly compared to the control group. Adult addicted men smoked Cannabis for different periods showed slight numerical increase in (ALP) activity with the increase of the length of the period of Cannabis smoking. In contrast the activity of the (ALT) and the (AST) reported significantly lower levels compared to the non smokers group [34].

In context of Protein total level cannabis abusers showed lower scores (M=5.58) in comparison with control group (M=9.97). Cannabis abusers showed lower scores in Albumin level (M=2.44) in contrast with control group (M= 4.54). In perspective of Globulin level of liver function test the cannabis abusers showed lower scores (M=2.03) in relation with control group (M=4.98). In perspective of A: G Ratio level the cannabis abusers showed lower scores (M=3.44) in comparison with control group (M= 6.71). Literature revealed that the concentrations of serum albumin, total protein, electrolytes and glucose were not significantly tainted by marijuana addiction. Serum concentrations of serotonin and 5-hydroxyl indole acetic acid (5HIAA) were extensively decreased although the serum levels of dopamine, noradrenaline and adrenaline were significantly increased.

The existence of precise cannabinoids (CB) receptors in mammalian tissues was first revealed by radioligand binding, and was followed by the molecular cloning of two G protein–coupled CB receptors [15]. CB1 receptors are mainly abundant receptors in the mammalian brain, but expressed in peripheral tissues, including various cell types of the liver, at much lower yet functionally applicable concentrations [22].

Conclusion

During the present study it was found that chronic cannabis abuse fabricate changes in some liver enzymes such as Aspartate amino transferase, Alinine amino transferase, Alkaline phosphate and Gamma glumutal transfersae . Abnormal range in these enzymes leads to destruction of red blood cells, hepatitis or cirrhosis, gall stones or blockage of bile duct, weaker immune system bone problems like rickets, osteomalacia, cardiovascular disorder, kidney diseases, lung cancer and testicular cancer rarely seen among chronic abusers. They should endow psychological therapies such as motivational assessment therapy, spiritual therapy, yoga, meditation, group therapy, family and deviant behaviors of the addicted group.

The evident and potential health implications for CUD is at odds with its historical standing as a typically benign substance, and this has been significantly compounded by the current lack of effective and tailored treatment avenues [31]. No evidence based pharmacotherapies are currently available neither for the management of cannabis withdrawal and cravings, nor for complex presentations where comorbid drug abuse is evident. Rather, consultants and mental health professionals working in the field help the abusers by taking the various medical tests so that a clear picture comes out and diagnosis will be easily evolved however implementation of brief cognitive behavioural therapy and contingency management have indicated the strongest evidence for success [32]; The religious leaders and society committees should take serious measures against drug peddling and usage of psychoactive substances in the societies by taking the assistance of J&K police department and collaborative drug de-addiction and rehabilitative centers to put away the youth of the valley [35-42].

Religion is the way to be protective against the use of cannabis [33]. The government should deploy the police force to stop cannabis cultivation and other drug peddling or trafficking in the valley and take prolific steps in construction of new Drug De-Addiction and Rehabilitation Centers for both the genders and formulate strategies of making seminars, debates, rallies

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and mental health programmes in every corporate so that awareness spreads among the common masses of Kashmiri valley. Now it would be more important for the government of J&K to engage the psychologists/counselors in education sector to assist the students in enhancing personality development and determining their future.

Acknowledgement

The author appreciates all those who participated in the study and helped to facilitate the research process.

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DOI: 10.19080/GJARM.2017.03.555605

How to cite this article: Irfan A W, Muzafer A K, Bhupinder S. Effect of Cannabis Abuse and Ezymatic Alterations to Endorse Liver Dysfunctions. Glob J Add & Rehab Med. 2017; 3(1): 555605. DOI: 10.19080/GJARM.2017.03.555605.