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Is Liver Fibrosis in Association with Opium Addiction and Intravenous Drug Abuse among Hepatitis C Virus-infected Patients?

Running Title: Liver Fibrosis, Opium Addiction and Intravenous Drug Abuse in HCV-infected Patients

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ABSTRACT

Introduction: Hepatitis C virus (HCV) infection is a prevalent etiology that leads to cirrhosis. Various factors affect liver fibrosis progression. In the current study, we aimed to assess the probable role of opium consumption and intravenous drug abuse (IVDU) on liver inflammation and fibrosis. **Materials and Methods**: This is a case-control study conducted on 58 patients with hepatitis C virus infection in 2012. Anti-HCV antibody and quantitative HCV-RNA burden were performed for all patients. Then, they underwent a liver biopsy for the determination of inflammation grading and liver fibrosis based on the Hepatic Activity Index (HAI). Regarding inflammation grade, patients were divided into two groups of 0-4 grade as controls and 5-18 as cases. Considering the fibrosis score, patients were divided into two groups of 0-2 score as controls and 3-6 score as cases. **Results**: This study was conducted on HCV positive patients; among them, 74.1% were smokers, and 53.4% were opium addicts. Regarding liver inflammation grading, 52.2% of cases and 25.7% of controls were IVDU and 65.2% versus 45.7% were opium addict (P-value=0.04 and 0.145, respectively). On the other hand, regarding fibrosis score, 60% of cases versus 50% of controls were opium addicts, while 30% of cases versus 39% of controls were IVDUs (P-value>0.05). **Conclusion**: Contrary to the previous studies, we found no association between opium addiction with either liver inflammation or fibrosis. Based on this study, IVDU was only associated with liver inflammation, but liver fibrosis.

INTRODUCTION

The most common underlying reason for cirrhosis lead to liver transplantation in the United States is the hepatitis C virus (HCV) infection, while in developing countries, the hepatitis B virus (HBV) infection is the most common reason (1). In patients with HCV infection, disease progression to end-stage liver disease, and eventually, cirrhosis is different from a patient to another due to virus type, host state, and environmental factors. Alcohol use and smoking as two environmental factors have been proved to affect hepatitis progression (2, 3).

About smoking, various mechanisms have been raised. As a cigarette consists of contents that induce increased production of inflammatory cytokines, thus satellite cells would be activated, and it progresses to liver fibrosis. On the other hand, cigarette causes increase in carboxy-hemoglobin indirectly and, therefore, tissue hypoxia, increased secretion of erythropoietin, polycythemia, and eventually hepatic tissue injury following increased iron burden (4, 5).

Theoretically, inhalator opium consumption can exacerbate tissue damage with similar mechanisms mentioned above. Besides, impurities such as lead and arsenic added to opium may affect liver damage negatively (6). The current study aims to assess the effects of opium consumption on liver tissue damage in hepatitis C.

MATERIALS AND METHODS

This is a case-control study conducted on 58 patients with hepatitis C virus infection referred to Taleghani Hospital (affiliated to Tehran University of Medical Sciences) in 2012.

Patients with confirmed HCV infection through anti-HCV antibody study were included.

Exclusion criteria were co-infection of HBV or HIV in a confirmed HCV patient, active alcoholism, and being under anti-viral therapy.

Consent forms for participating, and all needed information about the study were given to patients. This study was approved based on 10773 code from Research Council and Ethics Committee of School of Medicine of Isfahan University of Medical Sciences.

Patients' information was derived through an interview, paraclinical laboratory tests, patients' past medical records, and liver biopsy.

Anti-HCV antibody and quantitative HCV-RNA count were performed for all patients using the ELISA method and polymerase chain reaction method, respectively.

Then, all patients underwent liver biopsy in order to determine inflammation grading and liver fibrosis based on Hepatic Activity Index (HAI) (7). In order to achieve acceptable internal and external validity, a biopsy sample was taken adequately. Also, in order to eliminate intraobserver bias, all biopsies were studied by a reference pathologist.

Inflammation grading was divided into two groups of 0-4 grade as control patients and 5-18 as case ones. In addition, by considering the fibrosis score, patients were divided into two groups of 0-2 score as controls and 3-6 score as cases.

Then data were analyzed using the Statistical Package for Social Sciences (SPSS version 20) software. Descriptive data were reported in mean±standard deviation. For analytic data, independent T-test, paired T-test, Chi-square, and ANOVA were used. P-value of less than 0.05 was considered significant.

RESULTS

This study was conducted on 58 HCV positive patients with a mean age of 38.09±11.61 years old (range: 19-67 years), including 50 (86.2%) males and 8 (13.3%) females.

Among studied patients, 43 (74.1%) patients were smokers, and 31 (53.4%) ones were opium addicts.

Seventeen ones (29.3%) were informed about HCV infection following blood donation, and HCV was detected in 23 (39.7%) patients incidentally through laboratory check-ups. In general, 69% of patients found out their HCV infection incidentally. Forty-five patients (77.6%) had unknown genotype in their records, followed by 12% who had 1A genotype of HCV (Table 1).

The cases and controls comparison based on the liver inflammation grading showed significant older age among the control group as the mean age of cases with liver inflammation was 33.87±9.30 years (range: 22-53 years), and controls was 40.86±12.24 years (range: 19-67 years) (P-value=0.024). Also, a comparison of the two groups in terms of liver fibrosis score revealed a remarkable higher age of cases than controls; 42.45±10.44 years (range: 23-61 years) for cases and 35.79±11.65 years (19-67 years) for controls (P-value=0.037).

Table 2 is showing the effects of addiction and intravenous drug use on inflammation grade and fibrosis score of the studied population using ANCOVA analytic test.

DISCUSSION

Variety of risk factors that can affect the progression of hepatic failure among viral hepatitis affected patients has been investigated previously. These factors include age, obesity, male gender, race, alcohol consumption, and co-infection of HBV and HCV.

Recently, the relation of smoking with hepatitis C infection progression has been confirmed (8). In the study by Cecilia et al., liver fibrosis was assessed in the co-infection of HCV and HIV. Although they presented smoking as an influential factor in the progression of liver fibrosis in only HCV positive patients, they found no association between liver fibrosis and co-infection of HCV and HIV. Besides, Cecilia T. et al. presented the effects of the severity of smoking on liver fibrosis progression (9). In another similar study about the effect of alcohol use on liver fibrosis among co-infection of HCV and HIV, Erin M Kelly et al. presented no association(10), while Cecilia T. et al. found relation of recent alcohol use, during previous six months in particular, on liver fibrosis progression (9).

Besides, C Hézode et al. presented the effects of cannabis sniffing use on the progression of hepatic fibrosis in hepatitis C affected patients. They found that cannabinoid receptors as an independent factor can cause liver fibrosis among even healthy patients. In the following, they assessed risk factors of hepatic fibrosis in HCV infected patients who consumed various patterns of cannabis including daily, intermittent, and non-consumers and eventually represented cannabis as an independent risk factor of hepatic fibrosis progression in chronic HCV. On the other hand, routine daily use of cannabis affected patients more steeply than intermittent use. Another point was hepatic fibrosis rapidity that was associated with cannabis use added to other factors such as alcohol consumption, age of more than 40 years, and HCV genotype 3 (11).

As most of the viral hepatitis patients, HCV patients, in particular, are opium addicts in the community of Iran, the importance of this evaluation is better clarified (6).

In the study of Ahmad Shavakhy et al. in Iran, a significant association between opium addiction and hepatic tissue damage among both hepatitis C and hepatitis B patients was notified(6).

In the current study, we have excluded patients who were co-infected by HCV and HBV and/or HIV. This exclusion criterion can eliminate probable influential factors found in the studies of Cecilia T. et al. and Erin M Kelly et al. about the co-infection of HCV and HIV (9, 10). On the other hand, assessed cases and controls were significantly different in terms of age. We found that cases who had a worse condition of liver fibrosis were significantly older than controls, this can present the possible independent effect of age on fibrosis progression among HCV patients, a fact that has been represented previously, as well (12,

13), but results about hepatic tissue inflammation were contradictory vice versa. We have to confess that based on the mentioned results, no hypothesis can be made about the effects of age on our results, but it is one of the marked limitations of our study that we have not assessed HCV infection age of onset and also duration.

In this study, we did not detect a statistically significant association between opium addiction with whether hepatic inflammation grading or hepatic fibrosis score. These findings have been found while being an intravenous drug abuser was significantly in association with hepatic inflammation grading, but hepatic fibrosis score.

Although we found no association between opium consumption and liver inflammation and fibrosis state but similar to smoking, the following mechanism can be raised for the effects of opium on liver fibrosis. In this hypothesis, fibrosis progression and increased level of carboxy-hemoglobin following opium consumption can cause tissue hypoxia followed by erythropoietin secretion; thus polycythemia occurs, and by iron overload, hepatic failure would progress (6). On the other hand, impurities added to opium in order to make them weighted can have adverse effects on liver function leading to liver fibrosis. For instance, the presence of Arsenic in opium was associated with a higher rate of fibrosis (14, 15). In the other study, conducted in Iran, lead levels were considerably high in the consumed opium by addicts. Pathological studies have presented the association of high serum lead levels with active hepatitis considering the pathological aspects, including macro- and microvesicular hemosiderosis, cholestasis, and lymphocytic cholangitis (6, 16).

While we have not found any association between opium consumption and liver inflammation and fibrosis, these hypotheses seem rational, and our results are somewhat surprising.

The novel finding of our study was the association of intravenous drug abuse with liver inflammation grade.

Formerly, Lucy E. Wilson et al. assessed this association for the first time. In their cohort study, they evaluated HCV positive intravenous drug users for about four years, and liver biopsy was performed twice. Besides, within biopsy intervals, patients were assessed using FibroSURE, aspartate aminotransferase-to-platelet-ratio index (APRI), and alanine aminotransferase (ALT) markers. Eventually, they found significant liver fibrosis progression in a minority of their study population. In addition, they presented that markers used for liver fibrosis progression assessment were insignificantly associated with the progression of liver fibrosis (17).

Knut Boe Kielland et al. have presented a study about biopsies derived from intravenous drug abusers HCV positive patients. In their study, they presented significant septal fibrosis in HCV affected intravenous drug abusers, especially among those with a history of intravenous drug abuse for the least duration of 25 years (18).

LIMITATIONS

Lacking information about patients' duration of addiction, patients' duration of IV-drug abuse, and duration of HCV infection are the most considerable limitations of the current study.

CONCLUSION

Contrary to the previous studies, we found no association between opium addiction with either liver inflammation or fibrosis. Based on this study, IVDU was only associated with liver inflammation, but liver fibrosis.

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AUTHOR CONTRIBUTION

Mohammad Javad Ehsani Ardakani contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

Sina Sadeghian contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

Alireza Shavakhi contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

Ahmad Shavakhi contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

Mehrdad Khodabandeh contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

CONFLICT OF INTEREST

Authors of the current study present no conflict of interest in any stages of conducting this manuscript.

ETHICAL STANDARDS

This proposal of this study which met the Helsinki declaration criteria was proposed to the Ethics Committee of Isfahan University of Medical Sciences. After approval, the patients' were informed about the study protocols, reassured regarding the confidentiality of the obtained data and signed written form of participation in the study.

Table 1. The characteristics of the study population HCV infection

	Number	Percent
The way of awareness from HCV infection		
Blood donation	17	29.3
Check up	23	39.7
Icter/abnormal liver function test	8	13.8
Other	7	12.1
Unknown	3	5.2
HCV genotype		
1A	7	12.1
2A	2	3.4
1B	3	5.2
2B	1	1.
Unknown	45	77.6
Possible underlying etiology of HCV infection		
Blood transfusion	16	27.6
Tattooing	10	17.2
Intravenous drug abuse	21	36.2
Dentistry during previous years of positive HCV	13	22.4
Sexual contact	12	20.7

(Abbreviations; HCV: Hepatitis C virus)

Table 2. Effects of addiction and intravenous drug abuse on hepatic tissue damage

		Control	Case	*P*-value
Liver inflammation				
Intravenous drug abuse	Positive	9 (25.7%)	12 (52.2%)	0.04
	Negative	26 (74.3%)	11 (47.8%)	
Opium addiction	Positive	16 (45.7%)	15 (65.2%)	0.145
	Negative	19 (54.3%)	8 (34.8%)	
Fibrosis score				
Intravenous drug abuse	Positive	15 (39.5%)	6 (30%)	0.476
	Negative	23 (60.5%)	14 (70%)	
Opium addiction	Positive	19 (50%)	12 (60%)	0.468
	Negative	19 (50%)	8 (40%)	

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