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Short Communication: Examining Metabolic Profiles in Opioid-Dependent Patient

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ABSTRACT

Background: Drug abuse is a social burden and a public health disorder. Previous evidence suggested numerous illicit substances (e.g., opioids, amphetamines, cocaine, & cannabis) affect immune system functions, oxidative stress mechanisms, inflammatory cytokines, and reactive oxygen species production.

This study aimed to determine the extent of these metabolic parameters in opioid-dependent patients. We also compared these patients with a healthy control group.

Methods: This study was conducted in Amirie Clinic, Kashan, Iran. Plasma and serum samples from 50 illicit opioid users (study group) and 50 non-opioid users (control group) were studied. Metabolic levels for MDA, NO, TAC, GSH, Insulin, HOMA-IR, and hs-CRP were assessed in both research groups (N=100).

Results: There was a significant difference in the status of MDA (P=0.003), NO (P=0.01), TAC (P=0.003), GSH (P=0.001), insulin (P=0.04), HOMA-IR (P=0.02), and hs-CRP (P=0.001) between the study and control groups. Furthermore, there was a significant correlation among the duration of illicit opioid use and MDA concentrations (r=-0.424, P=0.002), as well as TAC levels (r=0.314, P=0.02).

Conclusion: The study results suggested metabolic profiles were impaired in the study group, compared to the controls.

1. Introduction

Opioid dependence and abuse are major health problems and social issues in developing countries. Opium is a major illicit drug in Iran [1], i.e., the largest frequency of drug addicts per capita globally. The number of opioid dependents in Iran is estimated to range from 2 to 4 million individuals [2, 3]. In 2012, the International Narcotics Control Board demonstrated >11% of Iranians abuse drugs and a minimum of 8% annual increase is expected in this area. Drug use is linked to socioeco-

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nomic complications, physical dependency, and significant mortality and morbidity [4, 5]. Three medications are approved by the USFDA for treating opioid dependence. These drugs are classified by their mechanism of action to agonist (methadone), partial agonist (buprenorphine), and antagonist (naltrexone) agents [6].

Metabolic syndrome, a constellation of several risk factors, including insulin resistance, obesity, hypertension, and dyslipidemia, predicts higher risks for developing diabetes mellitus type II, coronary heart disease, and cardiovascular disease, which all cause mortality [7-9]. Evidence indicates that frequent use of methadone and opium are linked to disturbances in the immune system, the upregulation of inflammatory markers, lipid peroxidation, the enhanced production of reactive oxygen species, and DNA damage [10-12]. ROS upregulates inflammatory cytokines and increases Matrix Metalloproteinase (MMP) activity [13]. Oxidative stress refers to damage to lipids, proteins, and DNA caused by elevated intracellular levels of Reactive Oxygen Species (ROS). Additionally, elevated ROS act as signaling molecules, i.e., redox biology that maintain physiological functions [14].

Opioids influence oxidative stress mechanisms in the brain. Previous studies have indicated oxidative stress could generate opioid dependence [15-17]. In a study, morphine enhanced lipid peroxidation in tissues, whereas heroin led to protein oxidation, oxidative DNA damage, and lipid peroxidation [18]. Opioids also affect the activity of antioxidant systems, as observed by decreased total antioxidant capacity in the blood sample of heroin dependents [19]. In mice brains exposed to heroin, a reduction was observed in the activity of antioxidant enzymes (e.g., catalase, superoxide dismutase, & glutathione peroxidase). Additionally, the ratio of glutathione to oxidized glutathione was reduced, leading to a reduction [20].

To our knowledge, no study has evaluated metabolic profiles in opioid-dependent patients. A better understanding of the contribution of metabolic parameters in opioid-dependent subjects could lead to devising pragmatic interventions for identifying those at risk of metabolic syndrome. Therefore, the present study aimed to investigate the metabolic profiles in opioid-dependent patients.

This study aimed to evaluate the levels of these metabolic profiles in opioid-dependent subjects and to compare them with a healthy group.

2. Materials and Methods

This was a case-control study. We included 100 individuals (50 illicit opioid users, & 50 controls), who were referred to Amirie Clinic in Kashan City, Iran. The control group included subjects without a history of drug abuse. The study inclusion criteria were as follows: age of 18-80 years, and illicit opioid use for more than a year. The study exclusion criteria included the presence of psychotic symptoms in the past 6 months, metabolic diseases, such as diabetes and neurological diseases, the presence of kidney, liver, hematologic, or thyroid diseases, Human Immunodeficiency Viruses (HIV), or other chronic physical illnesses, and unwillingness to participate in the research project.

At baseline, 7 mL of fasting blood samples were collected from each patient at the Kashan reference laboratory. Then, the collected samples were stored at -80°C until analysis. Besides, hs-CRP and insulin levels were quantified using Enzyme-Linked Immunosorbent Assay (ELISA) kit. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was determined according to the standard formula [21]. Total nitrite was estimated using Griess method [22], Total Antioxidant Capacity (TAC) by the ferric reducing antioxidant power method developed by Benzie and Strain [23], Total Glutathione (GSH) using the method of Beutler et al. [24], and Malondialdehyde (MDA) concentrations were determined by the thiobarbituric acid reactive substances spectrophotometric test [25], with inter- and intra-assay CVs of <5%.

The obtained data were analyzed using SPSS. Qualitative data were analyzed using a Chi-squared test. Moreover, the relationship between study variables was analyzed using Spearman's correlation coefficient. Quantitative data were analyzed using Independent Samples t-test. $P<0.05$ was considered significant in the present study.

3. Results

One hundred individuals were assigned into two groups of study (50 illicit opioid users) and control (50 non-opioid users). In total, 89 males and 11 females were included in this research. The Mean±SD age of the study participants was 40.9±11.6 years (age range: 21-86 years). The Mean±SD age of the study and control groups were 39.1±8.6 and 39.1±8.6 years, respectively (age range: 23-63 years). In the study group, the mean age of first illicit drug consumption was 22.4 years and the range and Mean±SD of the duration of illicit opioid use were 1-27 and 11.5±7.3 years, respectively. In the

Table 1. The levels of metabolic parameters **(n=50)**

Variables	(Mean±SD)		P1
	Study Group	Control Group	
MDA (µmol/L)	3.7±1.5	2.8±1.3	0.003
NO (µmol/L)	28.0±4.0	30.2±5.0	0.01
TAC (mmol/L)	796.2±242.2	929.4±183.1	0.003
GSH (µmol/L)	6.6±138.0	7.7±157.0	0.001
Insulin (µIU/mL)	10.0±3.7	8.6±3.7	0.04
HOMA-IR	2.8±1.4	2.2±1.0	0.02
Hs-CRP (mg/L)	8.4±3.8	6.0±3.8	0.001

1 Data obtained from the Independent Samples t-test.

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study group, 26 (52%) were opium or opium residues users, 8 (16%) were heroin users, and 16 (32%) were multi-substance users furthermore, the route of opioid administration were smoking (25; 50%), orally (7; 14%), smoking or orally (5; 10%), and mixed methods (13; 26%). The daily Mean±SD frequency of opioid use for the study group was 2.5±0.9 (range: 1-6 per day).

There was a significant difference in MDA (Mean±SD: 3.7±1.5 vs. 2.8±1.3 µmol/L, P=0.003), NO (Mean±SD: 28.0±4.0 vs. 30.2±5.0 mg/dL, P=0.01), TAC (Mean±SD: 796.2±242.2 vs. 929.4±183.1 mmol/L, P=0.003), GSH (Mean±SD: 6.6±138.0 vs. 7.7±157.0 µmol/L, P=0.001), insulin (Mean±SD: 10.0±3.7 vs. 8.6±3.7 µIU/mL, P=0.04), the homeostatic model assessment of insulin resistance (Mean±SD: 2.8±1.4 vs. 2.2±1.0, P=0.02), and serum high sensitivity C-reactive protein (Mean±SD: 8.4±3.8 vs. 6.0±3.8 mg/L, P=0.001) levels between the study and the control groups (Table 1).

There was a significant correlation among MDA and the duration of illicit opioid use concentrations (r=-0.424, P=0.002), as well as TAC levels (r=0.314, P=0.02) (Figure 1); however, it was not associated with NO, GSH, insulin, HOMA-IR, and hs-CRP levels (Table 2).

The levels of metabolic parameters were not statistically different based on the route of opioid administration or the type of the abused drug. Furthermore, the levels of metabolic parameters were not statistically different based on the frequency of daily use.

4. Discussion

The prevalence of metabolic syndrome has been reported to be high among alcohol and opioid dependants [9]. Additionally, abusing other drugs have been linked to different biochemical changes. The present study evaluated the levels of metabolic parameters in illicit

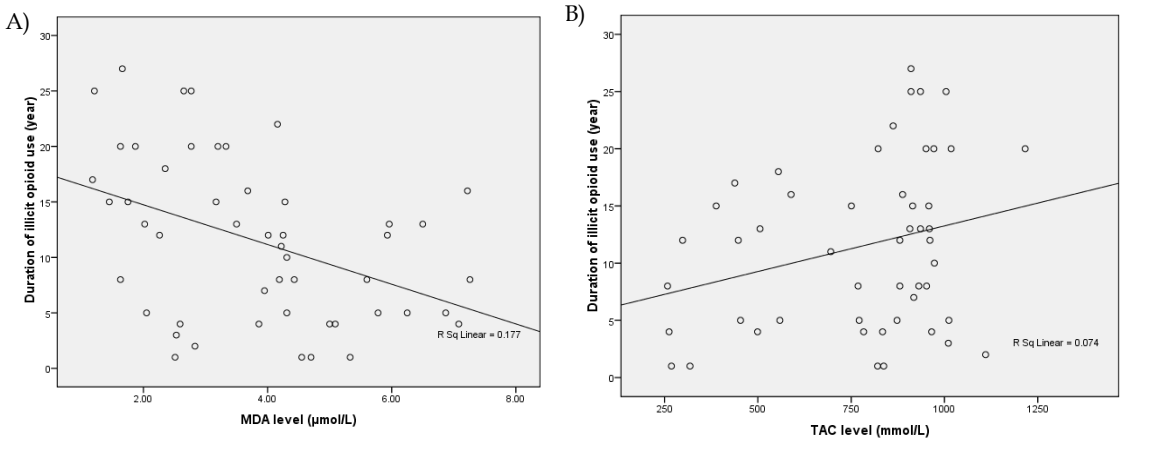

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Figure 1. The relationship between the duration of illicit opioid use and MDA and TAC levels (A, B)

Table 2. The relationship between the duration of illicit opioid use and the levels of metabolic parameters in the studied samples

Variable		r	P1
The duration of illicit opioid use	MDA (µmol/L)	-0.424	0.002
	NO (µmol/L)	-0.031	0.83
	TAC (mmol/L)	0.314	0.02
	GSH (µmol/L)	-0.053	0.71
	Insulin (µIU/mL)	0.106	0.46
	HOMA-IR	-0.096	0.50
	Hs-CRP (mg/L)	-0.068	0.63

1 Data obtained from Spearman's correlation coefficient.

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opioid users and compared their data with a non-opioid user group. We found a significant difference in the levels of metabolic parameters (e.g., MDA, NO, GSH, TAC, Insulin, HOMA-IR, & hs-CRP) between the research groups. This study was the first to assess the levels of metabolic parameters in opioid-dependent patients.

The collected results indicated exposure to opioids significantly decreases GSH, TAC, and NO levels, which probably increases the risk for metabolic syndrome. The oxidative metabolism of some drugs of abuse is a source for oxidative stress which generates ROS and reactive metabolites [26]. Salarian et al. [11] observed lower catalase and superoxide dismutase activities, and higher TNF-α and matrix metalloproteinase levels in illicit opioid users and those receiving methadone maintenance treatment. Furthermore, they detected an oxidative imbalance during the early days of transition from illicit opium use to methadone, as well as during methadone maintenance treatment [11].

Oxidative stress caused by exposure to drugs of abuse might derive from direct or indirect effects, and could occur after drug exposure [27]. Increased levels of oxidants, compared to antioxidant defense systems lead to the oxidation of proteins, DNA, phospholipids, cell dysfunction, and cell death [28].

Studies demonstrated the impact of oxidative stress in the induction of insulin resistance in peripheral tissues [29]. In our study, insulin and insulin resistance were higher in the study group. Moreover, heroin and methadone use may alter insulin sensitivity, glucose metabolism, and other hormones related to energy homeostasis [30], or increase fasting insulin levels [31]. Additionally, Odelia et al. indicated an association between abnormal glucose metabolism and opioid use; their clinical significance remains uncertain. However, the effects of opioids might compound the glucose intolerance presented in HIV-infected subjects with opioid dependence [32]. Opioid-induced insulin resistance may be coupled with β cell dysfunction. After an intravenous glucose load, heroin dependents presented a 42% lower acute insulin response, compared to the control subjects [30, 33]. Therefore, opioid use might provide multiple effects on metabolic and endocrine functions.

We found significant differences in MDA and hs-CRP levels between the study groups. Studies suggested that opioids could cause an inflammation response in the brain by inducing immune cells to release inflammatory molecules, called cytokines. Opioids-induced inflammatory markers were detected in the central amygdala, a brain region that has been strongly implicated in drug abuse, concerning its role in motivation and emotion [34, 35]. Dennis et al. [36] explored patients under methadone maintenance treatment with comorbid pain; they indicated elevated IFN-γ with higher levels of continued opioid dependence.

Furthermore, consistent with these results, it has been argued that opioid administration enhances the concentrations of malondialdehyde and a high-sensitivity CRP [11]. Chan et al. [12] demonstrated the production of inflammatory markers (e.g., IL-1β, IL-6, & IL-8) was significantly higher in MMT subjects, compared to healthy individuals. Another study reported that CRP levels were higher in the presence of nicotine, cannabis abuse, nicotine, and alcohol dependence [37]. Inflammation markers play a central role in the pathogenesis of metabolic syndrome and the development of cardiovascular disease [38]. Additionally, its possible correlates of inflammation, like exposure to stressors, serve as mediators, and increase the risk of drug use disorders [37]. Future

research is recommended to support the risk of metabolic disturbance linked to opioid use.

Our study had some limitations, including the small sample size; for more accurate results, larger sample sizes are recommended. In addition, most of the investigated subjects were males, and the relationship between gender and levels of metabolic parameters was not assessed. It is suggested to consider these factors in future studies.

5. Conclusion

The present research results indicated disturbances in some metabolic parameters in illicit opioid users. These findings suggested that opioids may induce metabolic syndrome. They obtained data signify the importance of establishing metabolic profiles as a routine assessment in illicit opioid users.

Ethical Considerations

Compliance with ethical guidelines

All procedures performed in studies involving human subjects were per the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments; also this study was approved by the Ethics Committee of Kashan University of Medical Sciences (Code: KAUMS. REC.96163).

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Author's contributions

All authors contributed in preparing this article.

Conflict of interest

The authors declared no conflicts of interest.

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