

## Original Article

# An Investigation of the Effects of Methadone and Buprenorphine on Liver Enzymes (AST, ALT, ALP) and Blood Sugar in Drug-Dependent Patients: A Clinical Examination

Vajihe Khodadadzade Benhangi<sup>1</sup>, Majid Rajabian<sup>2\*</sup>

<sup>1</sup>Department of Biological Sciences, Payame Noor University, Mashhad, Iran.

<sup>2</sup>Department of Biochemistry, Faculty of Biological Sciences, Payam Noor University of Iran, Tehran, Iran.

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## Abstract

**Background and Aim:** The present study aimed to investigate the effects of the long-term use of opioids drugs, particularly buprenorphine and methadone, on drug addicts. The primary focus was to examine the possibility of tissue and pathological lesions in the liver, as well as their impacts on liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and fast blood sugar levels (FBS) in these individuals.

**Materials and Methods:** For this clinical study, 264 drug-dependent patients were selected from Imam Reza Hospital and two addiction treatment centers. The patients were divided into two groups. They received treatment with varying doses of methadone and buprenorphine. The study consisted of two phases. The first phase investigated the relationship between liver enzymes and blood sugar levels, with the methadone dose before and after treatment, while the second phase explored hypotheses related to the effectiveness of methadone compared with buprenorphine.

**Results:** The results of this study revealed a significant correlation between the levels of liver enzymes, blood sugar, and methadone consumption. Higher doses of methadone were found to be more effective in detoxification and withdrawal compared with buprenorphine. In other words, the prolonged and high-dose use of methadone led to tissue and hormonal damage.

**Conclusion:** Using of high doses of methadone and its long-term usage have more detrimental effects on the health and tissues of drug addicts' bodies.

**Keywords:** Methadone, Buprenorphine, Liver, Liver enzymes, Blood sugar levels, Drugs

**\*Corresponding Author:** Vajihe Khodadadzade Benhangi, M.Sc., Biology Graduate, Faculty of Biological Sciences, Payame Noor University, Mashhad, Iran, Email: vkhodadadzade@gmail.com.

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## Introduction

Opioids are effective drugs used in the management of acute, chronic, and surgical pains (1). Commonly used opioids in this context include tramadol (39.0%),

methadone (27.6%), and triacodone (17.9%) (2). Methadone is a pure opioid receptor agonist that acts on Mu and Kappa receptors as agonists (3). Buprenorphine, on the other hand, is a partial agonist of Mu opioid receptor and a potent antagonist of Kappa

receptor (4).

Liver damage is one of the complications that may arise from opioid use (5). Enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) are crucial enzymes present in liver cells. Changes in their levels can indicate liver tissue damage and increased associated risks (6).

Regarding the opium use, it is commonly believed that it leads to a decrease in blood sugar levels. This decrease in blood sugar levels among opium addicts can be attributed to two reasons. Firstly, it may result from digestive issues caused by opium consumption such as constipation, reduced digestive enzymes, decreased pancreatic secretion, impaired food digestion, decreased stomach acid, and delayed passage of contents to the intestines. Additionally, opium addicts experience decreased appetite and consume less food, leading to reduced blood sugar levels even during fasting compared with normal individuals. Secondly, the lowering of blood sugar levels may be due to a direct hypoglycemic effect of morphine. Other studies have also indicated that morphine increases insulin secretion, insulin receptor expression, and cell metabolism, and reduces blood sugar-raising hormones such as corticosteroids and prolactin, consequently lowering blood sugar levels (7).

The use of opioids has paradoxical effects on the cardiovascular system, including atherosclerosis, increased lipid levels, decreased blood sugar levels, inflammation, arrhythmias, and increased blood pressure (8). The purpose of this article was to investigate the effects of methadone on the enzyme system, particularly on the levels of ALT, AST, and ALP enzymes, as well as blood sugar levels. This study was conducted with the aim of investigating the quantitative effects of methadone consumption on these enzymes and also investigating the new effects of methadone and buprenorphine on pain management of patients using these drugs.

## Materials and Methods

This research study aimed to investigate the effects of methadone and buprenorphine drugs on liver tests and blood sugar levels in drug addicts. The study was

conducted at Imam Reza Hospital (AS) in Mashhad and two addiction treatment centers affiliated to the Iranian Social Security Organization (Atlas, DIC) in 1400. The exclusion criteria for both the sample and control groups included non-use of other drugs, pregnancy, the age range between 25 and 80 years, and adherence to addiction treatment center protocols. The study population consisted of 264 individuals divided into two groups: the control group (47 drug-addicted individuals) and the experimental group (135 individuals treated with methadone and 26 individuals treated with buprenorphine). To measure blood sugar (FBS), the study population was further divided into two groups: the control group (39 patients without drug addiction) and the experimental group (17 drug-dependent patients after receiving methadone).

To calculate the sample size, the following equation was used:  $n = ((Z * \sigma) / E)^2$ .

- Z represents the desired standard deviation, which in this example is equal to 1.96 for a 95% confidence level.

- $\sigma$  represents the standard deviation of the investigated liver enzyme.

- E represents the acceptable sampling error, which in this example is equal to 0.1.

This research was conducted in two phases. In the first phase, liver tests, including ALT, AST, and ALP enzymes as well as blood sugar tests using FBS were performed using the relevant equipment. Blood samples were collected from the participants, and the levels of AST, ALT, ALP, and blood sugar were measured. In the second phase, the research hypothesis, which focused on the effectiveness of prescribing buprenorphine compared with methadone was investigated taking into account demographic variables such as age, gender, and physical and psychological complications after taking drugs (methadone and buprenorphine).

The participants were provided with necessary information and explanations, and after obtaining the informed consent, their basic characteristics and eligibility for the study were checked. Data analysis was conducted using SPSS statistical software, and descriptive statistics such as mean, standard deviation, and frequency distribution were calculated. A significance level of 0.05 was considered.

The results of the statistical analysis and the

comparison between the experimental and control groups indicated that methadone consumption had a significant effect on the liver tests and blood sugar levels of drug addicts. Due to the increase in the use of methadone and tramadol, this article aimed to raise the awareness of doctors about these drugs and their possible side effects.

## Results and Discussion

This study investigated the effects of methadone and buprenorphine, as the two main types of addiction treatment medications. In the first phase of the study, it was observed that methadone use resulted in a significant increase in ALT, ALP, and AST enzymes in the serum of the experimental group compared with the control group. Additionally, methadone consumption led to a significant decrease in FBS levels in the serum of the experimental group.

The second phase of the study revealed that buprenorphine use was more prevalent among men (83%) than women (17%), and the majority of users (57.4%) fell within the age group of 20-40 years. Regarding the dosage, 37.5% of buprenorphine users consumed doses between 3-6 mg, and 14.7% used doses of 6-9 mg. For methadone, 37.5% of users had doses of 12-14 cc, and 22.8% had doses less than 10 cc. Tablets were the most common dosage form for buprenorphine (40.4%), while juice was the primary form for methadone (72.36%). Users of both buprenorphine and methadone reported psychological factors such as tension, worry, anger, and internal tremor. Physical factors such as fatigue

and weakness were also commonly reported.

Among various methods of treating drug addicts, the use of methadone and buprenorphine in maintenance treatment centers has drawn attentions more than other methods (9). Methadone possesses both opioid and non-opioid properties. Firstly, it primarily binds to opioid receptors as a full agonist, thereby eliminating or minimizing withdrawal symptoms (10, 11). Secondly, it acts on the N-methyl-D-aspartate receptor for the treatment of hyperallergy and neuropathic pain. Thirdly, it may have an antidepressant effect by inhibiting the reabsorption of adrenaline and serotonin (12, 13). Various side effects of methadone, including dizziness, convulsions, weakness, chronic pain, bone and joint issues, sleep disorders, digestive disorders, low blood pressure, headaches, decreased libido, respiratory problems, and heart diseases have been reported (14, 15).

The liver, being the largest gland and one of the most important organs in the body, is involved in various functions such as synthesis, storage, and consumption of substances, as well as detoxification of foreign compounds (16, 17). The use of abusing drugs can lead to increased levels of aminotransferase (AST) and alkaline phosphatase (ALP) in the liver (18). Methadone is metabolized in the body, predominantly in the intestinal wall, through N-demethylation by CYP2B6, CYP3A4, and CYP2D6 enzymes, resulting in the formation of the inactive metabolite Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) (19). Methadone and buprenorphine are synthetic and semi-synthetic opioid drugs, respectively, which exhibit physiological and analgesic properties relatively similar to

**Table 1.** The Numbers Related to the Changes (mean±standard deviation) of Liver Enzymes and Blood Sugar.

IU/mL	AST	ALT	ALP	FBS
<b>Control</b>	18.80±5.62	16.00±6.35	234.00±45.15	119.37±42.52
<b>Patient</b>	26.36±7.73	25.54±8.36	283.30±62.57	106.00±32.87

**Table 2.** The investigation of paired t test in aspartate transferase, alkaline phosphatase, and alkaline transferase enzymes.

Variables (IU/ml)	Correlation	▲ Mean	t	▲ Std.Deviation	Sig
AST	0.113	7.56	5.14	2.11	0.00
ALT	0.016	9.54	5.82	2.01	0.00
ALP	0.236	49.30	2.61	17.42	0.02
FBS	-0.079	-13.37	-0.959	-9.65	0.353

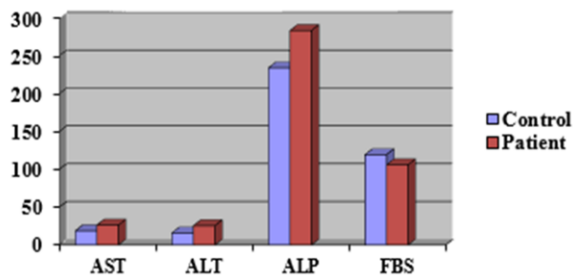


Figure 1. Average changes between the evaluated groups.

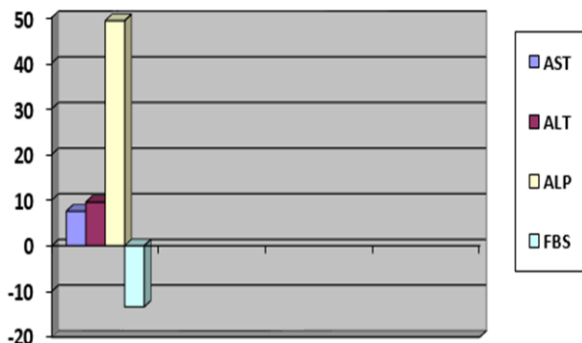


Figure 2. The average difference between the control and experimental groups.

opium, but with lower addictive potentials (20). Buprenorphine, derived from thebaine which is one of the natural phenanthrene alkaloids found in the poppy plant, acts as a partial agonist of the mu receptor and a potent antagonist of the kappa receptor (21). Its metabolism primarily occurs through the CYP3A4 enzyme when taken orally, and its active metabolite is norbuprenorphine (22). In comparison with methadone, buprenorphine offers advantages such as longer duration of action, reduced withdrawal syndrome, and less weight gain (23). However, the use of buprenorphine may be accompanied by side effects such as headache, dizziness, nausea, euphoria, constipation, caution, infection, and respiratory depression (24).

A study conducted by Boger *et al.* suggests that opioids like morphine and codeine, which are active metabolites, can accumulate in cases of renal dysfunction. Thus, lower doses should be prescribed to prevent further kidney damage. Buprenorphine, on the other hand, can be prescribed in the usual dose for patients with proper kidney function, as its pharmacokinetics remain unchanged in hemodialysis patients (25).

Methadone should be used for a short period and

gradually tapered off. Moreover, considering the fewer side effects of buprenorphine compared with methadone, buprenorphine can be a suitable alternative in opioid addiction treatment (11).

The increase of insulin after the peripheral injection of morphine can be justified in two ways. According to Reid, insulin and glucagon levels increase due to the presence of opioid receptors in the pancreatic islets, possibly their suppression of the secretion of pancreatic somatostatin, and the secretion of both hormones. According to Servit, in obese and diabetic models, the sensitivity of alpha 2-adrenergic receptors increases in some tissues, including pancreatic islets. Peripheral morphine compensates this increase in the sensitivity of alpha 2-adrenergic receptors by reducing the sympathetic flow, and increases the suppression of insulin secretion caused by these receptors (26).

## Conclusion

The recent study has several limitations. Firstly, there were differences in the interventions performed in SGPT and SGOT levels between the groups. However, the most significant and primary weakness of this study is the lack of examination of liver pathology. On the other hand, the present study also has its strengths. A meta-analysis on human samples, which is considered the most suitable type of study to establish a cause-and-effect relationship, was conducted in this study. By analyzing the results, the study provides a more comprehensive conclusion regarding the effect of methadone on blood insulin levels and certain liver enzymes, which are increased with the prolonged use of methadone. The reason for selecting a long-term course of methadone is that the drug leaves its harmful effects in the body during gavage.

Asgari *et al.* conducted a study on 360 diabetic patients to investigate the effect of opium on blood sugar control. They concluded that opium-addicted diabetic patients had higher HgA1C levels compared with others (27). In the study by Shirani *et al.*, however, the level of HgA1C was paradoxically lower, and opium-addicted individuals had a lower chance of developing diabetes and hypertension (28). When interpreting this issue, the influence of factors such as the small sample size should be taken into consideration. Furthermore, the effect of simultaneous use of narcotic and methadone on blood sugar levels

and insulin production needs to be considered. Furthermore, this research aimed to investigate the effectiveness of prescribing buprenorphine compared with methadone. It was found that prescribing a buprenorphine dose for the detoxification and withdrawal period was more effective than methadone, resulting in reduced hospitalization time and treatment costs. Shortening the detoxification period with buprenorphine could be a crucial step in overcoming opiate addiction, while the proposed method was not associated with increased side effects. These findings are consistent with the findings of the research conducted by Rose and Rose (2001, 2002), which was highly appreciated as a remedy involving one-time opioid detoxification using buprenorphine. The present study also echoes the findings of Kotz and Reznik (2001, 2002), who reported high success in opioid detoxification with a single prescription of a high dose of buprenorphine in two open clinical studies without a control group.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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