



Non-Invasive Detection of Opioid Addiction through Serum Analysis Using FTIR Spectroscopy

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Abstract

Introduction: Opioid addiction is a widespread chronic disorder associated with substantial morbidity and mortality worldwide. The impact of chronic opioid use on the serum biochemical profile remains incompletely understood. This study aimed to characterize serum biochemical profiles using Fourier Transform Infrared (FTIR) spectroscopy and evaluate their ability to differentiate opioid users from healthy controls.

Methods: Serum samples were obtained from control individuals (n = 40) and opioid use disorder (n = 30) patients. FTIR spectroscopy was performed to obtain serum spectral profiles. To evaluate spectral differences and group discrimination based on biochemical profiles, Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA) were applied.

Findings: FTIR spectra exhibited similar peak positions but significantly different absorbance values between groups. Phospholipid (1081 and 1246 cm⁻¹), amide (1321, 1543, 1636, and 3276 cm⁻¹), and lipid (1738, 2857, 2872, 2927, and 2957 cm⁻¹) bands showed reduced absorbance in the opioid group. Phospholipid absorbance at 1081 cm⁻¹ was significantly lower in opioid users than controls (P < 0.001). PCA demonstrated clear separation between groups, with the first three PCs explaining 97.34% of the total variance. HCA further confirmed distinct clustering by serum biochemical profile.

Conclusion: Our analysis successfully characterized serum biochemical alterations associated with opioid use disorder and effectively discriminated opioid users from healthy controls. The observed spectral differences confirmed the potential utility of FTIR spectroscopy as a rapid, minimally invasive approach for biochemical profiling and monitoring opioid-associated molecular changes.

Keywords: Opioid addiction, FTIR spectroscopy, Machine Learning, Serum biochemical analysis, Non-invasive diagnostics

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Introduction

Opioid addiction is a widespread chronic illness contributing to significant morbidity and mortality worldwide, causing relapse and remission throughout the patient's life.^{1,2} Opioid use disorder is primarily managed with pharmacological agents such as methadone and buprenorphine, which alleviate the severity of withdrawal symptoms and diminish drug cravings in dependent individuals. In cases of overdose or acute opioid intoxication, naloxone serves as the standard emergency treatment.³⁻⁵ Despite the availability of effective medications, opioid addiction remains challenging to manage, with high relapse rates documented even under

pharmacotherapy.⁵ Repeated opioid exposure induces neurobiological alterations that, together with withdrawal symptoms, contribute to the development of craving.⁶ The clinical heterogeneity of opioid use disorder may contribute to variability in disease progression and long-term outcomes, including relapse and remission.⁶

The development of physical dependence is driven by neuroadaptive changes induced by repeated opioid exposure.⁷ Several cellular processes are engaged when opioids are administered repeatedly, including enhanced signaling through cyclic AMP/protein kinase A and the cAMP response element-binding protein.⁸ In addition,



craving for the drug, impaired self-regulation, and exaggerated responses to drug-related stimuli appear to arise from molecular and cellular modifications in prefrontal cortex–basal ganglia glutamatergic pathways, such as disrupted G-protein signaling in the prefrontal cortex and enhanced presynaptic glutamate output in the accumbens^{9,10} Despite the pressing need to understand the biochemical impact of opioid administration, the specific chemical alterations in body fluids resulting from opioid use remain poorly understood. For nucleic acid analysis in genetic research, optical and vibrational spectroscopy techniques have found extensive application alongside conventional approaches. Fourier transform infrared (FTIR) spectroscopy, which is a vibrational spectroscopy method, stands out for its remarkable sensitivity to even the slightest changes in molecular structure.¹¹

FTIR spectroscopy is a powerful analytical tool that enables the detailed characterization of complex biochemical mixtures, such as blood serum.¹² This technique allows for the identification of various functional groups based on their unique vibrational frequencies, providing a comprehensive profile of the molecular composition.¹³

Specifically, the FTIR spectra demonstrated variations in phospholipids, amides, and lipid vibrations, with the control group showing higher absorbance values across most functional groups^{14,15} FTIR spectroscopy, combined with multivariate statistical analysis, offers a promising approach for detecting biochemical changes associated with diseases.¹⁶ The rationale for focusing on serum biochemical changes—rather than behavioral or neurobiological markers lies in the need for objective, easily accessible biomarkers that can complement clinical assessment tools.

For this reason, in the present study, FTIR spectroscopy was used to examine serum samples obtained from control subjects and from individuals with a history of opioid use, to clarify the biochemical alterations linked to opioid addiction. Principal Component Analysis (PCA) and Hierarchical Cluster Analysis (HCA) were additionally applied to distinguish the groups further on the basis of their spectral profiles.

Methods

Participants

This research received ethical approval from the Ethics Committee for Clinical Research of the Cerrahpaşa Medical Faculty, Istanbul University (Ethical code: E-83045809-604.01.02-137572), and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before enrollment. A specialist in substance use and mental health disorders performed the diagnostic assessment according to DSM-5 criteria, with the diagnosis supported by both blood testing and psychological examination. Venous blood was collected from 30 opioid use disorder patients at the time of hospital admission, before the initiation of any pharmacological treatment, while 40 healthy individuals served as controls. Inclusion criteria included participants to be regular opioid users, free of other chronic diseases,

and not using any additional medication before admission.

Sample preparation, FTIR measurements, and spectra analysis

Frozen serum samples were brought to a thawed state before being processed and measured. For each specimen, 4 µL of serum was pipetted onto the diamond ATR crystal and air-dried for 30 minutes at 25°C under controlled humidity so that measurement conditions remained uniform. Spectra were then recorded on a Nicolet IS50 FT-IR spectrometer, with OMNIC software configured to average 32 scans at 4 cm⁻¹ resolution over the 400–4000 cm⁻¹ region. Detection relied on a deuterated triglycine sulfate (DTGS) detector, and the Attenuated Total Reflectance (ATR) sampling technique with a diamond crystal was employed. A background spectrum preceded each measurement session, and the ATR crystal was cleaned with 70% ethanol between samples. Baseline correction and min–max normalization were performed using OMNIC software. Two spectral windows — 800–1800 and 2800–3000 cm⁻¹ — were selected for further evaluation because they contain the principal vibrational bands of serum biomolecules, namely proteins, lipids, and phospholipids. These regions, comprising 2493 data points per sample, were compared by one-way ANOVA with Tukey's post-hoc test at a significance level of $P < 0.05$; Tukey's procedure was preferred because it controls the familywise error rate arising from multiple pairwise comparisons among the groups. In addition, Principal Component Analysis (PCA) served to condense the dimensionality of the data while retaining most of the variance, thus allowing group differentiation to be visualized more readily.¹⁷ PCA was applied to mean-centered and vector-normalized FTIR spectra for the selected regions. Following computation of the first three PCs, sample clustering was visualized through score plots depicting PC1 vs. PC2, PC1 vs. PC3, and PC2 vs. PC3. Additionally, MATLAB R2022a was used to visualize PC loadings, providing insights into spectral bands driving differentiation between control and opioid-addicted groups. PAST 4.03 software was used to conduct Hierarchical Cluster Analysis (HCA).¹⁸ This technique relied on the Unweighted Pair Group Method with Arithmetic Mean (UPGMA) algorithm to organize the samples from both the control and the opioid-addicted groups according to their degree of similarity. Distances between samples were computed using the Euclidean similarity index, and a dendrogram was constructed to illustrate the hierarchical clustering of the samples.¹⁹

Results

FTIR spectroscopy was used to show chemical differences in the serum between control individuals and patients with opioid administration. Average spectra from both groups revealed vibrations originating from phospholipids (C–O stretching) at 1081 and 1246 cm⁻¹. Amide vibrations were visible at 1321 cm⁻¹ (Amide III), 1543 cm⁻¹ (Amide II), 1636 cm⁻¹ (Amide I), and 3276 cm⁻¹ (Amide A).²⁰ Furthermore, peaks corresponding from lipids vibrations (C=O and

CH_2 , CH_3 stretching, symmetric and asymmetric) were observed at 1738, 2857, 2872, 2927, and 2957 cm^{-1} .²¹ Lipid vibrations ($\text{C}=\text{O}$ and CH_2 , CH_3 stretching) were observed at 1738, 2857, 2872, 2927, and 2957 cm^{-1} (22). Functional groups from proteins and lipids (CH_3 wagging and $\text{C}=\text{O}$ symmetric stretching of COO^- groups) were also detected around 1395 and 1457 cm^{-1} .^{22,23}

Figure 1 (a) Mean $\pm$ SD FTIR spectra of serum samples obtained from the control (black) and opioid-administered (pink) groups over the 800–3500 cm^{-1} spectral range. Although both groups exhibited similar peak positions, the control group demonstrated consistently higher absorbance values across all spectral regions. In **Figure 1b**, the difference spectrum was generated by subtracting the mean opioid spectrum from the mean control spectrum. Positive values throughout the spectrum indicate higher absorbance in the control group, with the largest differences observed in the amide and lipid regions. Specifically, phospholipid absorbance at 1081 cm^{-1} was lower in opioid users (mean $\pm$ SD: 0.45 ± 0.05 AU) than controls (0.62 ± 0.07 AU; $P < 0.001$). Amide I absorbance at 1636 cm^{-1} was also significantly reduced in opioid users ($P < 0.01$). However, **Figure 1b** showed that a higher amount of each analyzed peak was visible in control patients. **Figure 1c** is the Mean $\pm$ SD absorbance values of phospholipids, amides, and lipids in the control and opioid-administered groups. Absorbance values for all three functional groups were significantly higher in the control group than in the opioid group ($*P < 0.05$). Finally, **Figure 1d** shows the ratios of

phospholipids to amides (P/A), phospholipids to lipids (P/L), and amides to lipids (A/L) in both groups. Compared with controls, the opioid-administered group exhibited a significantly lower P/A ratio and a significantly higher A/L ratio, indicating alterations in the biochemical balance among these molecular components ($*P < 0.05$).

Figure 2a displays the pairwise PCA score plots (PC1–PC2, PC1–PC3, and PC2–PC3), which demonstrate distinct patterns between serum samples collected from control and opioid-addicted groups using FTIR serum spectra spanning from 500 cm^{-1} to 3900 cm^{-1} . The PCA model utilizes three principal components (PCs), collectively explaining 97.34% of the data variation within this spectral range. Specifically, PC1 accounts for 65.35% of the variation, while PC2 and PC3 contribute to 21.50% and 10.49%, respectively. PC1 scores for control samples predominantly show positive values, while opioid-addicted samples exhibit primarily negative values. PC1's high variance likely reflects the lower phospholipid and protein content in opioid users, consistent with metabolic disruption caused by chronic opioid exposure. In contrast, PC2 and PC3 scores display a blend of positive and negative values across both groups. These findings suggest distinct spectral differences corresponding to the biochemical compositions of the two groups. The loading plots in **Figure 2b** illustrate how each spectral band contributes along the PC1, PC2, and PC3 axes within the 500–3900 cm^{-1} spectral region. These plots depict the relative importance of each spectral band in explaining the variance captured by each PC. Specifically,

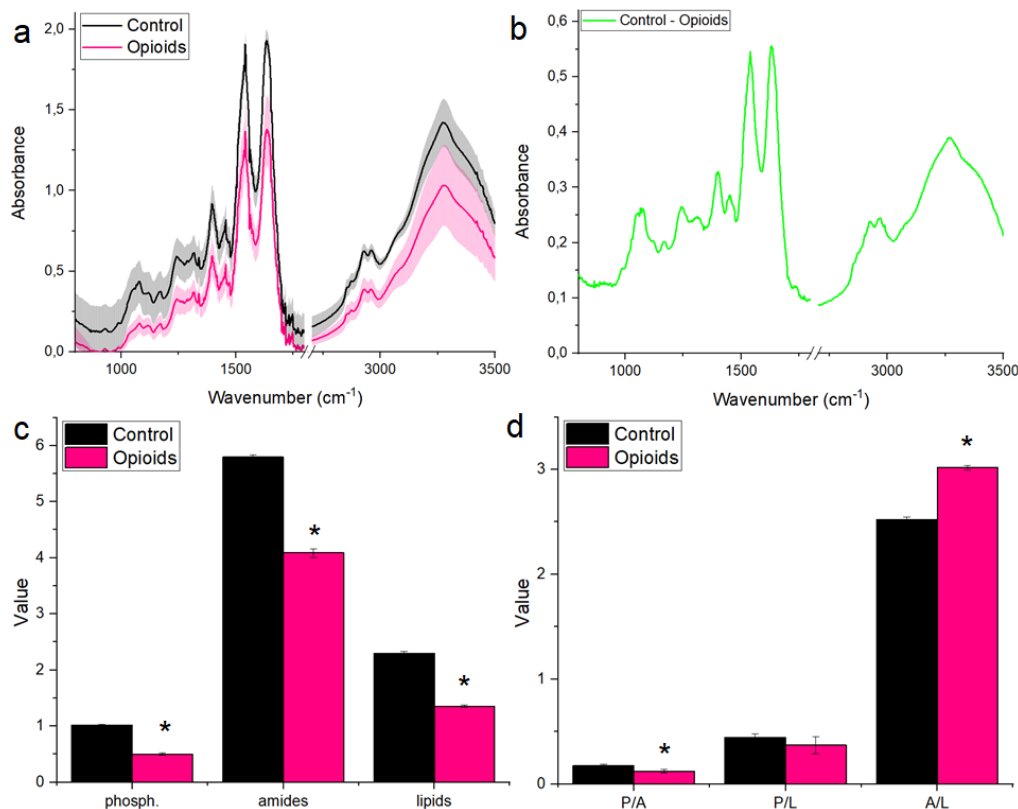


Figure 1. FTIR spectra of serum samples from controls and opioid administered patients, shown as mean $\pm$ SD (a); the difference spectrum between the two group averages (b); mean $\pm$ SD quantities of amides, phospholipids, and lipids (c); and the ratios of phospholipids to amides (P/A), phospholipids to lipids (P/L), and amides to lipids (A/L) in the two study groups (d)

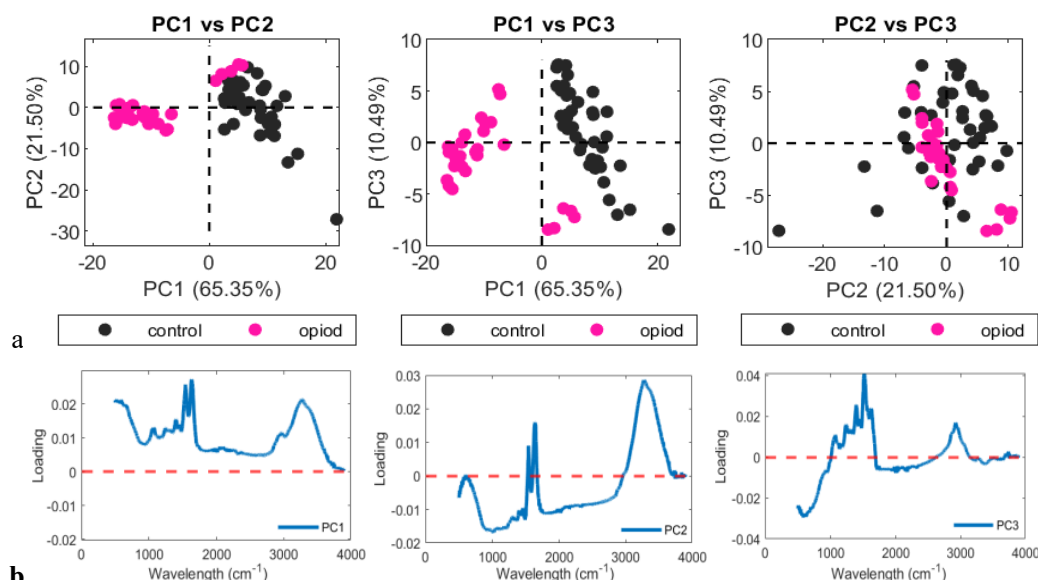


Figure 2. PCA score plots (a) with loading plots (b) of FTIR serum spectra for the 500-3900 cm⁻¹ spectral region

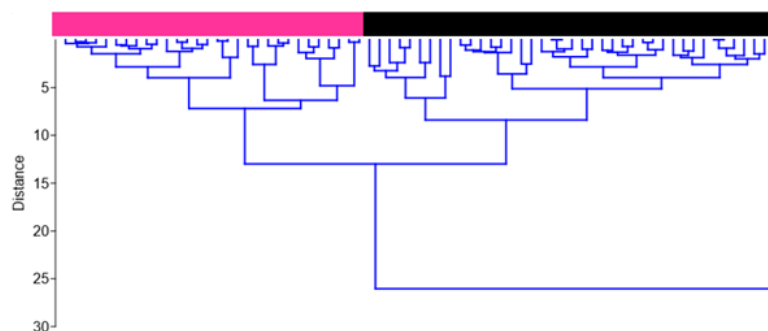


Figure 3. HCA analysis of FTIR serum spectra collected from control (black color) and opioid addicted groups (pink color)

positive values along with PC2 highlight contributions from phospholipid functional groups, amide III vibrations, and C=O lipid functional groups in both sample groups.

Figure 3 depicts clear clustering based on sample type (control vs. opioid-addicted groups) in the dendrogram generated by HCA. This distinct separation into similarity groups suggests that samples within each group exhibit greater similarity to each other than to samples from the opposite group.

Discussion

Opioids are effective analgesic agents widely used in clinical medicine; however, long-term use often leads to addiction and irreversible physiological changes^{24,25} Opioid-based medications may be involved in drug interactions, particularly in patients receiving multiple concurrent therapies, causing CNS depression and circulatory effects.²⁶ Opioid use is associated with significantly elevated risks of depression, overdose mortality, and other comorbidities. In this study, we aimed to characterize the chemical changes in serum caused by opioid administration and to evaluate whether it is possible to differentiate serum from control and opioid abused patients via FTIR spectroscopy.

FTIR spectroscopy is sensitive to molecular structural changes.²⁷ FTIR can detect even very small changes caused by opioids. In patients with opioid administration,

decreased absorbances of phospholipids, amides, and lipids were observed. Rezaei et al. reported that opioid use is associated with reduced low-density lipoprotein (LDL) levels and increased triglyceride concentrations, consistent with the lipid-related alterations observed in our FTIR spectra (Figures 1a and 1c).²⁸ Kazemi et al. similarly reported lower LDL and total cholesterol in opioid-abusing patients versus controls.²⁹ Similar changes in serum lipid profiles have also been reported in previous studies examining the effects of opioid administration.³⁰ Given that opioids act on protein receptors in neural tissue,³¹ variability in the protein fraction visible in FTIR spectra is expected. Divsalar et al. showed that gamma-globulin concentration in serum of opioid-administered patients was lower than controls,³² which is consistent with our findings of reduced protein-related absorbance.

From a mechanistic perspective, chronic opioid exposure likely disrupts membrane phospholipid composition through altered lipid metabolism pathways and receptor-mediated signaling. The decreased amide absorbance may reflect reduced globulin and albumin levels due to compromised liver function or altered protein synthesis secondary to long-term opioid use. The phospholipid-to-amide ratio changes observed here further suggest shifts in the balance between membrane lipid components and serum proteins, which may serve as a sensitive indicator

of opioid-related metabolic dysregulation.

The PCA score plots revealed significant separation between groups, with PC1 (65.35% variance) primarily reflecting biochemical differences in phospholipids, amides, and lipids. The HCA dendrogram further confirmed the distinct biochemical clustering. These results are consistent with previous FTIR studies on substance-related biochemical alterations^{33, 34}. Additionally, the loading plots indicate that phospholipid functional groups, amide III vibrations, and C=O lipid functional groups are the primary contributors to the observed spectral variance.

The distinct clustering patterns observed in the HCA dendrogram further confirm the efficiency of FTIR spectroscopy in distinguishing between serum samples from control vs opioid abuse groups. The separation into two clear similarity groups in the dendrogram suggests that the biochemical changes induced by opioid use result in consistent and detectable alterations in the serum's spectral profile, which aligns with previous studies that have reported biochemical modifications in body fluids due to substance abuse, underscoring the robustness of FTIR spectroscopy in identifying and characterizing such changes.¹²

The observed decrease in absorbance values for phospholipids, amides, and lipids in the opioid-addicted group versus the control group suggests that opioid use may lead to a reduction in these critical biochemical components. This reduction could be indicative of altered metabolic processes, membrane composition, or protein expression levels associated with chronic opioid use. Such alterations might result from the direct effects of opioids on cellular structures and functions or secondary to the body's response to prolonged drug exposure.

Compared to alternative diagnostic approaches, FTIR spectroscopy offers advantages of speed, no labeling requirement, and simultaneous profiling of multiple biomolecular classes. While mass spectrometry provides greater molecular specificity and ELISA offers quantification of individual biomarkers, the FTIR's low cost and minimal sample preparation make it attractive for clinical monitoring, particularly for relapse surveillance in outpatient settings.

The sample size (n=70) is modest and limits generalizability. The cross-sectional design precludes longitudinal insights into biochemical dynamics across stages of addiction or recovery. Future studies should include larger, diverse cohorts with longitudinal follow-up, and explore integration of FTIR with other analytical modalities to enhance diagnostic precision.

Conclusion

Taken together, the results underline the promise of FTIR spectroscopy as a robust, noninvasive diagnostic approach to identify the biochemical alterations that accompany opioid addiction. By offering a dependable means of distinguishing control subjects from opioid-addicted individuals through serum analysis, this technique may support the early recognition, follow-up,

and clinical management of substance use disorders. The clear separation patterns emerging from PCA and HCA constitute convincing evidence that FTIR spectroscopy coupled with multivariate analytical methods might effectively discriminate serum specimens according to their biochemical profiles. Subsequent work should aim at enlarging the sample size and investigating the biochemical mechanisms responsible for the spectral differences reported here, so that the method can be further validated and refined for clinical use. Combining FTIR spectrometry with complementary analytical techniques would additionally deepen our understanding of the specific molecular changes linked to opioid addiction and thereby open the way to more targeted and effective treatment strategies.

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Competing Interests

The authors declare that they have no conflict of interest.

Data Availability Statement

Data can be made available on reasonable request.

Ethical Approval

The study was approved by the Ethics Committee for Clinical Research of the Cerrahpaşa Medical Faculty of Istanbul University (Ethical code: E-83045809-604.01.02-137572), and was in accordance with the Declaration of Helsinki. Every participant in the study gave their signed, informed consent.

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