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Original Article

Associations Between Metabolic and Atherogenic Indices and Opioid Addiction: A Cross-Sectional Study From Kerman Coronary Artery Disease Risk Factors Study (KERCADRS)

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Abstract

Introduction: Opioid addiction is a major public health issue globally and in Iran. Chronic opioid abuse is linked with metabolic disturbances including dyslipidemia and insulin resistance (IR), increasing cardiometabolic risk.

Methods: In this cross-sectional investigation, we assessed the relationship between opium addiction and its associated metabolic and atherogenic factors in 92 adult participants. Participants were divided into two groups: addicts (n=38) and non-addicts (n=54). Data on baseline characteristics, including age, anthropometric indices (BMI, weight, height, waist circumference (WC)), lipid profiles, blood pressure (BP), and fasting blood sugar (FBS), were collected and compared between groups. Marital status and smoking habits were also assessed. Various metabolic and atherogenic indices were calculated and analyzed.

Results: Among the participants, no significant differences were observed between addicts and non-addicts in most anthropometric or lipid profile parameters. However, addicts had significantly higher FBS levels and a greater prevalence of smoking. The TyG index was also higher among addicts, suggesting increased IR in this group. Logistic regression analysis identified smoking and elevated FBS as independent predictors of addiction, even after adjustment for confounding variables.

Conclusion: This study highlights smoking and elevated FBS as significant independent predictors of addiction. The observed higher TyG index in the addict group may indicate underlying metabolic dysfunction. These findings underscore the importance of screening for metabolic disturbances in individuals with opioid use disorder.

Keywords: Opioid-related disorders, Metabolic syndrome, Insulin resistance

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Introduction

Opioid use disorder is a chronic, relapsing condition marked by persistent drug-seeking behavior, tolerance, and withdrawal symptoms, affecting millions worldwide.[1,2] According to recent estimates, nearly 62 million people worldwide used opioids in 2019, with approximately 36.3 million having opioid use disorder (OUD). Iran's geographical position exacerbates its severe drug use crisis. Sharing a border with Afghanistan, the world's largest opioid producer, Iran functions as the main transit corridor for drug trafficking into Europe. The World Health Organization (WHO) reports that opioid use in Iran exceeds the global average by threefold.[3]

Metabolic syndrome (MetS) encompasses a constellation of interrelated cardiometabolic risk factors, including abdominal obesity, abnormal lipid profile, hyperglycemia, and increased blood pressure, all of which significantly increase the risk of developing cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM).[4,5] It is projected that by 2030, approximately 578 million people worldwide will be affected by glucose metabolism disorders, particularly T2DM.[6] These disorders not only substantially impair patients' health-related quality of life but also impose a considerable economic burden on healthcare

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systems.[7] Multiple factors, such as unhealthy lifestyle habits, inadequate physical activity, poor dietary patterns, and substance use, contribute to the development and progression of glucose metabolism disorders.[8]

Previous investigations have documented contradictory and conflicting findings on the prevalence of MetS and related metabolic parameters among individuals with opioid addiction. Some evidence suggests potential benefits, such as lower body weight, reduced adiposity, and improved lipid profiles, possibly due to appetite suppression, altered fat distribution, or other mechanisms associated with chronic opioid use.[9,10] In contrast, other studies indicate adverse effects, including elevated triglycerides (TG), glucose dysregulation, IR in non-diabetic contexts, and increased cardiovascular risk factors.[9,11] For instance, opioid agonist therapies showed differential effects, with buprenorphine often linked to lower MetS rates compared to methadone.[11] In opioid-specific contexts, it was reported that opioid addiction significantly reduced serum adiponectin levels, which may contribute to impaired metabolic regulation given adiponectin's protective anti-diabetic and anti-atherogenic roles.[12] Furthermore, Masoomi et al. reported significantly elevated serum homocysteine concentrations in opioid-dependent people compared to non-addicted controls, identifying another independent cardiovascular risk factor in this population.[13] These inconsistent findings, ranging from potential protective metabolic effects to heightened risks of dyslipidemia, IR, and CVD, highlight the complex and controversial impact of chronic opioid use on cardiometabolic health, particularly in high-prevalence settings like Iran.

Given these inconsistent metabolic profiles and the heightened cardiometabolic risks observed in some opioid-addicted individuals, surrogate markers of IR and atherogenic risk such as the triglyceride-glucose (TyG) index, atherogenic index of plasma (AIP), cardiometabolic index (CMI), lipid accumulation product (LAP), abdominal volume index (AVI), and atherogenic index (AI) offer valuable non-invasive tools to assess these risks more comprehensively.[14-16] The TyG index, in particular, correlates strongly with hyperinsulinemic-euglycemic clamp measures of IR.[17,18] Similarly, AIP predicts cardiovascular events, while LAP reflects visceral fat accumulation.[19,20] These indices have been validated in diverse populations for detecting MetS, IR, and related complications. However, they remain understudied in the context of opioid addiction, where direct assessments using conventional parameters have yielded conflicting results, and few studies have applied these precise composite markers to clarify the net impact of chronic opioid use on glucose homeostasis, lipid metabolism, and overall cardiometabolic health. It was indicated that approximately 36% of patients with Coronary Artery Disease (CAD) in Iran are opioid addicts.[21] The cardiovascular and lipid profile effects of opioid consumption appear to vary considerably depending on the duration, dosage, and intensity of use, according to multiple investigations. For example, it was reported that opioid use disorder is linked with increased susceptibility to cardiovascular mortality.[22] In contrast, alternative evidence, including findings reported by Marmor et al, has suggested a potentially cardioprotective effect associated with opium use.[23] Similarly, the literature on lipid profile alterations remained divided, with some studies reporting significant reductions, others demonstrating elevations, and still others finding no appreciable differences in the opioid-using population.[24-26]

However, the majority have been restricted to conventional lipid and glucose parameters or narrowly defined clinical subgroups rather than these precise, non-invasive composite markers. Given the well-documented interindividual variability in human metabolic responses to opioids and the unique cultural-geographical context of opioid consumption in Iran, such gaps highlight the necessity for targeted, population-specific investigations. Accordingly, the present cross-sectional study, conducted within the framework of the Kerman CAD Risk Factors Study (KERCADRS), aimed to fill this critical void by systematically examining the associations between these up-to-date indices and opioid addiction status.

Methods

Study Design and Participants

The present cross-sectional analysis utilized baseline data derived from the KERCADRS, a prospective population-based cohort study that has been ongoing in Kerman, southeastern Iran, since 2009. In this study, we recruited 92 adults who participated in KERCADRS between 2021 and 2023. Based on their opioid use history, participants were allocated into two distinct categories: (1) individuals diagnosed with opioid use disorder according to DSM-5 criteria, with active substance use within the preceding month (n = 38), and (2) healthy controls with no self-reported lifetime history of opioid consumption (n = 54). Exclusion criteria included acute illness, pregnancy, malignancy, or use of medications affecting metabolism (e.g., corticosteroids, antipsychotics).

All KERCADRS participants provided written informed consent at enrollment, acknowledging the study protocols and authorizing the publication of de-identified questionnaire responses and laboratory data. Personal identifying information was anonymized and maintained in strict confidence. Our study protocols were approved by the Ethics Committee of Kerman University of Medical Sciences (Ethical Approval code: IR.KMU.REC.1403.597).

Data Collection

- Demographic data (age, sex, marital status), high-risk behaviors (smoking status and detailed history of opioid use), and medical history were collected through face-to-face structured interviews using a pre-designed questionnaire. Physical activity levels were evaluated using the WHO Global Physical Activity Questionnaire (GPAQ), which captures activity across three life domains: at home, at work, and during leisure/recreational time. Activity intensity was expressed in

metabolic equivalent of task (MET) units, with one MET defined as the resting energy expenditure of an average adult (approximately 3.5 mL O_2/kg/min).[27] For GPAQ score interpretation, we calculated total weekly physical activity in MET-minutes by applying standard MET coefficients: 4.0 METs for moderate-intensity activities (including walking) and 8.0 METs for vigorous-intensity activities across three domains: work, travel, and recreational activities. The aggregate physical activity volume presented the summation of MET-minutes across all three domains. Based on the WHO guidelines, participants' physical activity levels were stratified into three categories: High physical activity: Individuals achieving at least 1500 MET-minutes/week of vigorous activity or a combined total of at least 3000 MET-minutes/week across any intensity.

- Moderate physical activity: Individuals achieving at least 600 MET-minutes/week of total physical activity, or at least 20 minutes of vigorous activity per day for 3 days, or at least 30 minutes of moderate activity per day for 5 days.
- Low physical activity: Individuals who did not meet the criteria for either high or moderate categories, representing a sedentary or insufficiently active lifestyle.

Anthropometric measurements (height, weight, WC, and Hip Circumference (HC)) and blood pressure (BP) were obtained from all participants by a physician following standard clinical protocols. Hypertension was characterized by systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or current antihypertensive pharmacotherapy.[28] Smoking status and opioid use were collected via self-report. BMI was calculated as weight (kg) divided by height squared (m^2). Fasting blood samples (after at least 12 hours of overnight fasting) were collected and analyzed at a central laboratory to measure FBS. Low-Density Lipoprotein Cholesterol (LDL-C) was estimated using the Friedewald formula as follows: LDL-C = TC − HDL-C (TG/5).[29] Lipid profiles were assayed using specific enzymatic kits on an autoanalyzer (Hitachi 912, Roche Diagnostics).

Calculation of Metabolic and Atherogenic Indices

The following indices were computed[10,15]:

- AIP: log [TG/HDL-C]
- TyG: ln [TG (mg/dL) × FBS (mg/dL)/2
- CMI: TG/ HDL-C × WHtR (waist-to-height ratio)
- AI: (TC - HDL-C)/HDL -C
- TyG-WC: TyG × WC (cm)
- TyG-BMI: TyG × BMI
- LAP: (WC-65) × TG/100 for men; (WC-58) × TG/100 for women
- AVI: $[2 + (WC/10)^2 + 0.7 \times (HC\text{-}WC)/10^2]/1000$
- LCI = [TC × TG × LDL-C] / HDL-C

Statistical analysis

In the present study, the Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Data conforming to a normal distribution were summarized as mean ± standard deviation (SD), while non-normally distributed variables were expressed as median with interquartile range (IQR). Categorical data were reported as frequencies and percentages. The independent t-test, Mann-Whitney U test, the Chi-squared test, and Fisher Exact text were used to evaluate differences among groups. Multivariable logistic regression with backward stepwise selection was employed to examine the potential relationships between demographic variables, biochemical markers, and addiction outcome. Variables with a P value < 0.20 in univariate analyses were entered into the multivariable model. A liberal significance threshold was applied to reduce the likelihood of excluding variables that may become important after adjustment for other covariates in the multivariable analysis. Statistical significance was defined as a P value < 0.05. All statistical analyses were performed using SPSS version 24.

Results

Ninety-two participants were included in the analysis and categorized into two groups: Addicts (n = 38, 41.3%) and non-addicts (n = 54, 58.7%).

Baseline characteristics

Table 1 summarizes baseline characteristics of participants according to addiction status. A total of 38 individuals (41.3%) were classified as addicts and 54 (58.7%) as non-addicts. Age and anthropometric measures, including BMI, weight, height, and WC, did not differ significantly between groups. Similarly, lipid profiles (cholesterol, LDL-C, HDL-C, TG) and BP (systolic and diastolic) showed no significant variation ($P > 0.05$).

However, FBS levels were higher among addicts [median 125 mg/dl (IQR 98.75)] compared with non-addicts [median 101 mg/dl (IQR 32)] ($P = 0.007$), suggesting poorer glycemic control in the addicted group. A significant difference was also observed in marital status: the proportion of married participants was lower among addicts ($P = 0.03$).

Cigarette smoking was markedly more prevalent among addicts (36.8%) compared to non-addicts (7.4%) ($P < 0.001$). Other drug consumption, physical activity levels, and diabetes treatment whether insulin or oral drug use did not differ significantly between groups ($P > 0.05$). Male predominance was observed in both groups (71.1% vs. 66.7%), with no significant sex-related difference.

Metabolic and atherogenic indices

Table 2 presents the comparison of metabolic and atherogenic indices between addict and non-addict groups. The mean AIP values did not differ significantly between the groups ($P > 0.05$).

In contrast, the TyG index was significantly higher among addicts compared to non-addicts (8.96 ± 0.66 vs. 8.64 ± 0.58; $P = 0.01$), suggesting a higher degree of insulin resistance in the opioid-addicted group, as reflected by the significantly elevated TyG index. For other composite indices, including

Table 1. Comparison of Clinical and Demographic Characteristics Between Addict and Non addict Groups

Addict	Yes	No	*P* value
N (%)	38 (41.3)	54 (58.7)	
Age [years, median (IQR)]	60 (9.25)	62 (12.25)	0.81
BMI [kg/m², mean (SD)]	24.14 (3.87)	25.09 (3.03)	0.21
Weight [kg, mean (SD)]	65.21 (11.99)	67.79 (11.82)	0.31
Height [cm, mean (SD)]	164.24 (9.89)	164.05 (9.95)	0.92
WC [cm, mean (SD)]	89.78 (11.2)	91.59 (8.46)	0.41
Cholesterol [mg/dl, mean (SD)]	172.86 (38.66)	181.38 (41.99)	0.33
LDL-C [mg/dl, mean (SD)]	104.30 (32.34)	111.43 (34.82)	0.32
Systolic BP [mmHg, median (IQR)]	110 (25)	110 (10)	0.64
Diastolic BP [mmHg, median (IQR)]	70 (20)	70 (10)	0.37
FBS [mg/dl, median (IQR)]	125 (98.75)	101 (32)	0.007
Triglyceride [mg/dl, median (IQR)]	114.5 (70.75)	106.5 (94)	0.67
HDL-C [mg/dl, median (IQR)]	43.5 (15.75)	45 (17.25)	0.61
Sex n (%)			
Male	27 (71.1)	36(66.7)	0.65
Female	11(28.9)	18 (33.3)	
Other-Drug-consumption			
Yes	30 (78.9)	38 (70.4)	0.35
No	8 (21.1)	16 (29.6)	
Marital status, n (%)			
Married	31 (37.3)	52 (62.7)	0.03*
Single	7 (77.8)	2 (22.2)	
Smoking n (%)			
Yes	14 (36.8)	4 (7.4)	<0.001
No	24 (63.2)	50 (92.6)	
Physical Activity n (%)			
Low	15 (39.5)	17 (31.5)	
Moderate	14 (36.8)	26 (48.1)	0.55
Intense	9 (23.7)	11 (20.4)	
DM- DRUG n (%)			
Yes	20 (52.6)	26 (48.1)	0.67
No	18 (47.4)	28 (51.9)	

*Independent t-test performed for normally distributed continuous variables (BMI, weight, height, WC, cholesterol, LDL-C), the Mann-Whitney U test for non-normally distributed continuous variables (age, systolic BP, diastolic BP, FBS, TG, HDL-C), and the Chi-squared test for categorical variables (sex, marital status, smoking, physical activity, other drug consumption, DM_INSU, DM_DRUG). Data are presented as mean ± SD for normally distributed variables and median (IQR) for non-normally distributed variables. Abbreviations: BMI, body mass index; BP, blood pressure; FBS, fasting blood sugar; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; IQR, interquartile range; SD, standard deviation; TG, triglycerides

TyG-WC, TyG-BMI, CMI, AVI, and LAP, there were no significant differences ($P > 0.05$).

Multinomial logistic regression analysis

The results of univariable and multivariable logistic regression analyses investigating potential predictors of addiction status are summarized in Table 3.

The results of univariable and multivariable logistic regression analyses investigating potential predictors of addiction status are summarized in Table 3. In bivariable analysis, smoking status and FBS were significantly associated with addiction. Participants who smoked had higher odds of being addicts (OR = 7.29; 95% CI: 2.16–24.52; $P = 0.001$), and each unit increase in FBS was linked to greater odds of addiction (OR = 1.02; 95% CI: 1.01–1.03; $P = 0.001$). The TyG index also showed a positive association (OR = 2.31; 95% CI: 1.14–4.67; $P = 0.02$).

After adjustment for potential confounders, including age, sex, BMI, marital status, and other drug consumption, only smoking and FBS remained statistically significant. Smokers were approximately 14 times more likely to be addicts compared with non-smokers (AOR = 13.99; 95% CI: 3.02–64.74; $P < 0.001$), and higher FBS levels continued to predict addiction (AOR = 1.03; 95% CI: 1.01–1.06; $P = 0.002$). Other variables, including BMI, physical activity, lipid profile parameters, BP, diabetes medication, and atherogenic indices (TyG-WC, TyG-BMI, LAP, AVI, CMI, AI, AIP), showed no significant associations in either unadjusted or adjusted analyses ($P > 0.05$).

Table 2. Metabolic and atherogenic indices in the study population

Addict	Yes	No	*P* value
N (%)	38 (41.3)	54 (58.7)	-
AI [mean (SD)]	2.45 (0.85)	2.53 (0.86)	0.69
AIP [mean (SD)]	0.41 (0.18)	0.38 (0.26)	0.57
TyG [mean (SD)]	8.96 (0.66)	8.64 (0.58)	0.01
TyG-WC [mean (SD)]	805.54 (122.84)	792.29 (97.71)	0.56
CMI [median (IQR)]	1.40 (1.18)	1.31 (1.24)	0.51
TyG-BMI [median (IQR)]	223.53 (79.41)	214.8 (51.67)	0.76
AVI [median (IQR)]	1.65 (1.15)	1.6 (1.4)	0.49
LAP [median (IQR)]	34.67 (29.8)	31.63 (32.26)	0.99

*Independent t-test performed for normally distributed continuous variables (AI, AIP, TyG, TyG-WC) and the Mann-Whitney U test for non-normally distributed variables (CMI, TyG-BMI, AVI, LAP). Data are expressed as mean ± SD for normally distributed and median (IQR) for non-normally distributed variables. Abbreviations: AI, atherogenic index; AIP, atherogenic index of plasma; AVI, abdominal volume index; CMI, cardiometabolic index; IQR, interquartile range; LAP, lipid accumulation product; SD, standard deviation; TyG, triglyceride-glucose index; TyG-BMI, triglyceride-glucose × body mass index; TyG-WC, triglyceride-glucose × WC

Discussion

The present cross-sectional study investigated the association between opioid addiction and several metabolic and atherogenic indices in an Iranian adult population. Overall, most anthropometric parameters, lipid profile variables, and BP measures were similar between the two groups and did not differ significantly. However, FBS and the TyG index were significantly higher among addicts. In multivariable logistic regression analysis, smoking and FBS remained independently associated with addiction.

Previous studies have reported heterogeneous metabolic outcomes among opioid users.[9,11] Elman et al.[11]compared metabolic outcomes in patients receiving opioid agonist medication-assisted treatment, specifically buprenorphine versus methadone. Their findings showed that patients treated with buprenorphine had significantly lower rates

Table 3. Bivariable and multivariable logistic regression analysis of factors associated with addiction among study participants

Variable		OR (95% CI)	*P* value	AOR (95% CI)	*P* value
Age- year		1.01 (0.96;1.06)	0.61		
BMI- kg/m²		0.92(0.81;1.04)	0.18	1.007 (0.843;1.204)	0.935
Gender	Female	1			
	Male	1.22 (0.49;3.02)	0.65		
Physical activity	Low	1			
	Moderate	0.61 (0.23;1.57)	0.31		
	Intense	0.92(0.3;2.84)	0.89		
Systolic-BP (mmHg)		0.99 (0.96;1.02)	0.59		
Diastolic-BP (mmHg)		0.97 (0.93;1.02)	0.32		
Other-Drug-Consumption	No	1			
	Yes	1.57(0.59;4.18)	0.35		
Smoking	No	1		1	
	Yes	7.29(2.16;24.52)	0.001	13.99 (3.02;64.74)	<0.001
FBS – mg/dl		1.02(1.01;1.03)	0.001	1.03 (1.01;1.06)	0.002
DM-INSU	No	1			
	Yes	1.07 (0.226;5.089)	0.93		
DM-DRUG	No	1			
	Yes	1.19 (0.521;2.747)	0.67		
Cholesterol mg/dl		0.99(0.98;1.01)	0.32		
TG mg/dl		1	0.94		
HDL-C mg/dl		0.98(0.94;1.03)	0.58		
LDL-C mg/dl		0.99(0.98;1.01)	0.32		
TyG		2.31(1.14;4.67)	0.02	0.68 (0.21;2.21)	0.52
LAP		0.99 (0.977;1.01)	0.47		
AVI		0.93 (0.67;1.30)	0.69		
TyG-WC		1.001(0.99;1.005)	0.562		
TyG-BMI		1 (0.989;1.01)	0.99		
TG-HDL-C Ratio		0.963 (0.748;1.23)	0.768		
CMI		0.893 (0.584;1.36)	0.599		
LCI		1	0.41		
AIP		1.68 (0.28;10.03)	0.568		
AI		0.904 (0.555;1.475)	0.68		

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; FBS, fasting blood sugar; AI, atherogenic index; AIP, atherogenic index of plasma; AVI, abdominal volume index; CMI, cardiometabolic index; LAP, lipid accumulation product; LCI, lipid cholesterol index; TyG, triglyceride-glucose index; TyGBMI, triglyceride-glucose × body mass index; TyGWC, triglyceride-glucose × waist circumference. Variables with $P<0.20$ in the bivariable analysis were entered into the multivariable logistic regression model

of MetS and more favorable HDL-C levels compared with those receiving methadone. In contrast, methadone exposure was associated with lower HDL-C concentrations, higher TG, increased mean arterial pressure, and elevated fasting glucose and HbA1c. Although that study did not evaluate composite indices such as AIP or CMI, the observed alterations in lipid and glycemic parameters highlight the complex metabolic consequences of opioid exposure.

In contrast to our finding that BMI was similar between addicted and non-addicted individuals, Byanyima et al.[9] reported significantly lower BMI and body weight among opioid users. This inconsistency may reflect differences in dietary patterns, duration and intensity of opioid use, socioeconomic status, and demographic characteristics between the study populations. While chronic opioid use often leads to malnutrition and weight loss in certain cohorts, our study population may represent a stage or pattern of use where gross anthropometric parameters have not yet been significantly altered.

Evidence from clinical studies further suggests that metabolic consequences may differ according to treatment modality and type of opioid exposure.[9,11] These findings highlight the complex metabolic effects of opioid exposure and suggest that different opioid agents, addiction treatment modalities, and clinical settings may exert distinct cardiometabolic influences.

Our findings regarding glycemic status align with a comprehensive meta-analysis reporting heterogeneous glucose responses among human opioid users, contrasting with consistent hyperglycemic outcomes in animal models.[30] These modest and varied alterations in cross-sectional designs are often attributed to the short-term metabolic effects of opioids.[31] Mechanistically, acute activation of opioid receptors can modulate intracellular signaling pathways (e.g., PI3K/Akt and AMPK), which may transiently increase peripheral glucose uptake and suppress hepatic glucose production.[32] However, chronic opioid exposure likely triggers distinct physiological adaptations, potentially contributing to the dysregulation of glucose homeostasis over time.

In the present study, systolic and diastolic BP did not differ significantly between addicted and non-addicted individuals. Conversely, Hamrah et al. reported elevated BP levels among opioid-dependent individuals.[33] Whereas Sobhani et al. observed lower BP and a reduced prevalence of hypertension among opioid-using patients with CAD.[34] These discrepancies may stem from differences in opioid dosage, duration of use, and population characteristics. Mechanistically, acute or lower-dose opioid exposure can reduce BP via vasodilation and decreased sympathetic activity; however, prolonged use may trigger adverse cardiovascular adaptations—such as oxidative stress, endothelial dysfunction, and elevated homocysteine levels—potentially leading to hypertension.

In our study, serum triglyceride levels did not differ significantly between addicted and non-addicted individuals. However, conflicting and inconsistent results have been reported in the literature regarding lipid alterations. In contrast to our findings, Sobhani et al. reported significantly lower triglyceride levels among opioid-consuming patients with CAD. This discrepancy

highlights that the metabolic impact of opioids may heavily depend on the clinical characteristics of the study population; while Sobhani's study focused exclusively on high-risk patients with established CAD, our cohort represents a more general sample from the KERCADRS study. Such variations in the underlying health status of participants might alter how chronic opioid exposure influences lipid metabolic pathways.[34] Additionally, Asgary et al.[35] and Fatemi et al.[24] observed elevated triglyceride concentrations in healthy non-opioid users compared with opioid-consuming individuals. Furthermore, these discrepancies could be due to differences in sample sizes, study designs, and coexisting behavioral risk factors among the participants, such as smoking, high rates of physical inactivity, and specific dietary changes, including increased sugar consumption or malnutrition, which are frequently observed in individuals with opioid use disorder and can independently alter lipid metabolism.

Among the composite cardiometabolic indices evaluated in the present study, the TyG index was significantly higher among addicted individuals, suggesting a greater degree of IR in this group. However, other indices, including AIP, CMI, TyG-WC, TyG-BMI, AVI, and LAP, were not significantly different between addicted and non-addicted participants and were not independently associated with addiction in regression analyses. Previous research has suggested that opioid exposure, particularly methadone therapy, may influence lipid metabolism and cardiometabolic risk factors, including reductions in HDL-C and elevations in TG.[11] In contrast, a 6-month methadone treatment study demonstrated a significant increase in serum TG levels compared with baseline, while cholesterol levels remained unchanged.[36] Furthermore, in a preclinical study, 10 days of methadone administration significantly lowered HDL cholesterol and raised LDL cholesterol in both male and female rats, while triglyceride levels decreased in male rats.[37] Nevertheless, the overall evidence remains inconsistent, and some studies have reported relatively favorable lipid profiles or lower prevalence of MetS in certain opioid-using populations.[9]

Contrary to the findings of Sobhani et al.,[34] who observed reduced levels of AIP, TyG index, and non-HDL-C cholesterol among CAD patients using opioids, our results from a community-based sample did not replicate this pattern, a discrepancy potentially driven by inter-cohort clinical heterogeneity. On the other hand, although conducted on alcohol consumers rather than opioid users, the study by Baek et al.[38] demonstrated in a Korean population that the TyG index was significantly higher among both smokers and alcohol consumers, showing a synergistic adverse effect on this surrogate marker of IR. While our study demonstrated that both opioid addiction and smoking were individually linked to metabolic alterations, evaluating the definitive synergistic effect of combined smoking and opioid consumption on the TyG index was precluded in our study due to the limited sample size, which would compromise statistical power in subgroup analyses. Nevertheless, smoking, which was markedly more prevalent among our addicted participants, is well known to induce systemic inflammation, oxidative stress, and impair insulin signaling. Therefore, the high prevalence of smoking in the addicted group may act as an overlapping behavioral risk factor that worsens glycemic control and elevates the TyG index, a critical relationship that warrants dedicated evaluation in future large-scale longitudinal studies.

Compared with some previous reports, our study showed relatively modest differences in anthropometric and lipid parameters between addicted and non-addicted individuals. Prior literature has suggested that opioid users may exhibit lower body weight or altered metabolic patterns due to appetite suppression, changes in energy expenditure, and the metabolic effects of chronic opioid exposure.[9,10] Nevertheless, the lack of significant differences in several composite cardiometabolic indices in our analysis suggests that the metabolic impact of opioid use may be heterogeneous and influenced by contextual factors such as smoking behavior, dietary habits, and regional characteristics. These variations highlight the importance of considering population-specific contexts when interpreting cardiometabolic findings in opioid-using populations.

The present study has certain limitations, notably its cross-sectional nature and the relatively small number of participants, both of which could have compromised statistical power for identifying subtle disparities in select metabolic and atherogenic indices across the study groups. Additionally, reliance on self-reported information regarding substance use may introduce the possibility of under-reporting due to social stigma or fear of disclosure, potentially leading to misclassification bias. These factors should be considered when interpreting the findings of the present study.

Furthermore, the cross-sectional design precludes establishing causal relationships between opioid use and cardiometabolic indices. The absence of direct measures of IR, such as HOMA-IR or the euglycemic hyperinsulinemic clamp, also limits mechanistic interpretation. Therefore, the TyG index was used as a surrogate marker. Future studies are recommended to include direct measurements of insulin resistance. Additionally, potential confounding factors, including detailed dietary intake, exact opioid dose, duration, and route of use, and genetic susceptibility, were not fully assessed and may have influenced the observed associations. Future longitudinal studies with larger and more balanced samples, including sufficient numbers of individuals in recovery, are needed to better clarify the temporal relationship between opioid exposure and cardiometabolic risk. Incorporating comprehensive dietary assessments, repeated biomarker measurements, and direct assessments of insulin sensitivity would help further elucidate metabolic changes across active use, abstinence, and recovery phases in opioid-using populations, particularly in high-prevalence settings such as Iran.

Conclusion

In conclusion, the present study suggests that opioid addiction is associated with alterations in certain

metabolic parameters, particularly higher FBS and an elevated TyG index, which may reflect increased IR and impaired glucose metabolism among addicted individuals. However, most composite atherogenic indices, including AIP and other related markers, did not differ significantly between addicted and non-addicted groups and were not independent predictors of addiction after multivariable adjustment. Cigarette smoking emerged as a strong independent factor associated with addiction, highlighting the potential combined influence of substance use behaviors on metabolic health. These findings underscore the importance of considering metabolic screening, particularly for glucose-related abnormalities, in populations with opioid use. Further large-scale longitudinal studies are needed to clarify the causal pathways linking opioid use, smoking, and cardiometabolic risk and to better understand how these relationships evolve during addiction and recovery.

Authors' Contribution

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Competing Interests

The authors declare that they have no competing interests.

Consent for Publication

Not applicable.

Data Availability Statement

The datasets generated and/or analyses during the present study are available from the corresponding author on reasonable request.

Ethical Approval

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The protocol was reviewed and approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (Ethical Approval Code: IR.KMU.REC.1403.597).

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