Current Addiction Reports (2023) 10:581–593
https://doi.org/10.1007/s40429-023-00493-4

Metabolic Profiles Associated with Opioid Use and Opioid Use Disorder: a Narrative Review of the Literature

Juliana I. Byanyima[1] · Xinyi Li[1] · Sianneh A. Vesslee[1] · Henry R. Kranzler[1] · Zhenhao Shi[1] · Corinde E. Wiers[1]

Accepted: 2 May 2023 / Published online: 19 May 2023

Abstract

Purpose of Review Opioid use disorder (OUD) is a chronic, relapsing condition that is epidemic in the USA. OUD is associated with serious adverse consequences, including higher incarceration rates, impaired medical and mental health, and overdose-related fatalities. Several medications with demonstrated clinical efficacy in reducing opioid use are approved to treat OUD. However, there is evidence that medications for OUD cause metabolic impairments, which raises concerns over the long-term metabolic health of individuals recovering from OUD. Here, we summarize the scientific literature on the metabolic effects of the use of opioids, including medications for treating OUD.

Recent Findings Our findings showed lower body weight and adiposity, and better lipid profiles in individuals with OUD. In individuals with diabetes mellitus, opioid use was associated with lower blood glucose levels. In contrast, among individuals without underlying metabolic conditions, opioids promoted insulin resistance. Treatment of OUD patients with the agonists methadone or buprenorphine caused weight gain, increased liking and intake of sugar, and impaired lipid profile and glucose metabolism, whereas treatment with the antagonist naltrexone demonstrated evidence for reduced sweet preferences.

Summary Our findings highlighted a gap in knowledge regarding the safety of medications for OUD. Further research is needed to determine how best to reduce the risk of metabolic disorder in the treatment of OUD with opioid agonists versus antagonists.

Keywords Addiction · Dependence · Heroin · Medication · Metabolism · Nutrition

Introduction

The current opioid epidemic is a major public health problem that stemmed from the over-prescription of opioids in the late 1990s before their addictive properties were fully characterized [1]. Between 1999 and 2010, prescriptions for opioid pain relievers, such as hydrocodone, codeine, and oxycodone, quadrupled and substantially increased opioid-related overdose deaths [1]. The opioid epidemic has since been exacerbated by the advent of highly potent synthetic opioids, such as fentanyl [2]. Opioid use disorder (OUD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as a problematic pattern of opioid use leading to clinically significant impairment or distress, which may include the development of opioid tolerance, opioid withdrawal symptoms, opioid craving, and/or a persistent desire or unsuccessful efforts to cut down or control opioid use [3]. Therefore, OUD is associated with adverse socioeconomic, psychiatric, and health consequences that reduce the quality of life in affected individuals [4].

While the detrimental effects of opioid use have been well studied, much research has focused on the neuropathophysiology of addiction, and no extensive review of metabolic dysfunctions in individuals with OUD has been published. Furthermore, although medications for OUD with opioid agonists (e.g., methadone and buprenorphine) and antagonist (e.g., naltrexone) have proven clinical utility in curbing opioid misuse [5] and preventing overdose-related fatalities [6], there is emerging evidence that these medications may

Juliana I. Byanyima and Xinyi Li contributed equally to this work.

✉ Zhenhao Shi
zhshi@pennmedicine.upenn.edu

✉ Corinde E. Wiers
corinde.wiers@pennmedicine.upenn.edu

[1] Center for Studies of Addiction, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, 3535 Market St. Suite 500, Philadelphia, PA 19104, USA

cause metabolic dysfunction [7]. Here, we summarize the scientific literature to identify the metabolic consequences of medications for OUD and the potential need for modifications in OUD treatment strategies.

Metabolic syndrome (MetS) is a cluster of signs associated with an increased risk of cardiovascular disease and diabetes. Diagnosis of MetS typically involves meeting at least three of the following five criteria or taking a prescription medication to manage the associated symptoms: (1) waist circumference ≥ 88/102 cm (females (F)/males (M)), (2) triglyceride ≥ 150 mg/dl, (3) high-density lipoprotein (HDL) level < 50/40 mg/dl (F/M), (4) blood pressure > 130/85 mmHg, and (5) fasting glucose ≥ 100 mg/dl. Diagnostic criteria vary slightly across advisory organizations. The National Cholesterol Education Program Adult Treatment Panel III requires a minimum of three criteria without further specification, while the International Diabetes Federation diagnostic criteria require individuals to present with central adiposity (i.e., high waist circumference) and two of the other four MetS symptoms. Recommendations from International Diabetes Federation additionally stipulate a lower central adiposity threshold of waist circumstance of ≥ 80/94 cm (F/M) [8–10].

Individuals with MetS often experience chronic pain that necessitates the use of prescription opioids and thus are at a higher risk of developing OUD than non-MetS individuals. For example, neuropathic pain is a common complication of diabetes [11], while opioid use may produce physiological adaptations that contribute to the development of MetS [7]. In this review, we will examine the effects of OUD and medications for OUD on each of the five MetS signs and discuss possible mechanistic pathways that underlie OUD-associated metabolic dysfunction. We identified articles on OUD, opioid use, and metabolic syndrome between August 2021 and April 2024 using PUBMED and Google Scholar and included additional studies listed in the reference sections of relevant articles. We only considered articles written in English. Articles presented in this review comprised studies of synthetic/semisynthetic opioids (i.e., heroin) and naturally derived opioid (e.g., morphine, crude opium [Teriak], and opium sap [Shireh]). Given the variations in study populations and diagnoses, we used the terms "individuals with OUD" or "individuals who use opioids" based on whether a diagnosis of OUD is defined in the article being considered.

Being overweight or obese has been associated with an increased risk for metabolic and cardiovascular diseases and various cancers [12]. However, there is growing evidence to support the notion of the "obesity paradox," in which higher body mass index (BMI) was associated with reduced mortality, suggesting that individuals with obesity/elevated BMI do not necessarily have obesity-related health consequences [13]. Furthermore, weight stigma has been found to have profound negative psychological and physiological consequences [14, 15]. While acknowledging the importance of discussing the health implications of BMI status, this review will solely focus on the role of opioid use in the development and perpetuation of MetS.

Metabolic Syndrome

The prevalence of MetS among individuals who use opioids varies widely across studies from 5.1 [9] to 56% [16], likely due to between-study differences in MetS diagnostic criteria, types of opioids used (crude opium [Teriak] vs. synthetic opioid [heroin]), administration of medications for OUD (whether administered and, if so, its type, dosage, and duration), study location, and participant characteristics (Table 1). In studies of inpatients with OUD that did not specify whether medications for OUD were used, MetS prevalence ranged from 5.1 [9] to 29.3% [7]. A study that included both individuals who occasionally used opioids and individuals with OUD showed a modestly higher MetS prevalence in both opioid-using cohorts (39.0–39.6%) than

Table 1 Prevalence of metabolic syndrome in individuals who use opioids

Country of study	*N*	MOUD	MetS diagnostic criteria	MetS prevalence (%)
India [9]	59	NS	IDF	5.1
India [9]	59	NS	NCEP ATP III	20.3
India [7]	41	NS	IDF	29.3
Iran [17]	811	NS	IDF	39.0
Iran [17]	811	NS	NCEP ATP III	39.6
Spain [18]	122	Methadone	NCEP ATP III	29.5
USA [16]	26	Buprenorphine	AHA	19.2
USA [16]	32	Methadone	AHA	56.3

AHA, American Heart Association; *IDF*, International Diabetes Federation; *MOUD*, medication for opioid use disorder; *MetS*, metabolic syndrome; *NS*, not specified; *NCEP ATPIII*, National Cholesterol Education Program Adult Treatment Panel III

those who never used opioids (36.4–37.2%) [17]. Using the International Diabetes Federation diagnostic criteria for MetS, current opioid users had significantly higher odds of MetS than non-users after adjusting for gender, age, BMI, and cigarette smoking. However, no significant difference was observed when the diagnostic criteria from the National Cholesterol Education Program Adult Treatment Panel III for MetS were applied, likely attributable to the overdiagnosis of MetS in the non-user group [17].

In individuals undergoing buprenorphine treatment for OUD, 19.2% met the study-specified criteria for a MetS diagnosis compared to 29.5–56.3% of individuals receiving methadone [16, 18]. Binary logistic regression for MetS diagnosis demonstrated that longer exposure to methadone, but not buprenorphine, was associated with greater odds of developing MetS. Furthermore, the length of methadone use was positively correlated with blood serum levels of triglyceride, HDL, and glucose [16, 18]. Given the increasing prevalence of MetS in the current obesogenic environment and its associated comorbidities, cognizance of the metabolic effects of OUD medications can help in selecting the best treatment options.

Metabolic Signs: Anthropometric Measurements

Diagnostic criteria for MetS stipulate waist circumference. However, due to the paucity of opioid studies that referenced waist circumference, we utilized anthropometric measurements (i.e., BMI) as proxies. Although BMI highly correlates with waist circumference ($R = 0.78$, $p < 0.01$) [19] and is widely used due to ease of measurement, it is important to note that it does not provide information on the distribution of adipose tissue or muscle mass [20].

Several lines of evidence showed that individuals with substance use disorders, including alcohol, methamphetamine, and opioids, have lower body weight than the general population [21–24]. One study examined individuals with substance use disorder from a clinical trial network and compared them to an age-, sex-, and race-matched general population sample from National Health and Nutrition Examination Survey. Individuals with OUD had a lower BMI (24.9 kg/m^2, respectively) than those with stimulant use disorder (28.1 kg/m^2) and the general population sample (29.0 kg/m^2, respectively) [21]. An anthropometric study revealed that individuals who smoke or inject heroin had 3.8% and 5.0% less body fat, respectively, than those who do not [24].

Opioid agonist therapies methadone and buprenorphine are highly effective treatments for OUD and are often associated with weight gain. In a prospective study, the BMI of patients undergoing methadone maintenance treatment increased from 22.5 to 24.3 kg/m^2 at the first follow-up (~270 days from baseline) and 25.9 kg/m^2 at ~840 days from baseline [25]. Other studies of methadone treatment showed that females gained more weight than males [26] (recently meta-analyzed in [27]) and changes in BMI occurred concomitantly with changes in body composition. Specifically, body fat increased from 25.3 ± 10.0 to 30.6 ± 9.3% and muscle mass decreased from 71.0 ± 9.6 to 65.8 ± 8.9% within 1 year of initiating methadone treatment [28]. Buprenorphine demonstrated similar weight-inducing effects as methadone. In one study, 4 months of buprenorphine/naloxone treatment was associated with significant weight gain, from 63.86 ± 8.78 to 68.49 ± 8.65 kg [29]. In a comparison of methadone and buprenorphine treatments, both groups exhibited similar anthropometric characteristics, supporting the idea that methadone and buprenorphine produce similar weight-inducing effects [16].

Antagonism of opioid receptors with naltrexone is another effective approach of OUD treatment [30]. The oral formulation of naltrexone in combination with bupropion has been shown to reduce body weight and is approved by the Food and Drug Administration for obesity management under the trade name Contrave® [31]. However, studies examining the weight-reducing effects of naltrexone monotherapy have yielded mostly null results [32, 33]. Although first approved as an oral formulation for OUD treatment, naltrexone is also available as a monthly extended-release intramuscular injection (XR-naltrexone). To the best of our knowledge, only one study examined weight changes in naltrexone-treated OUD patients. The study compared body weights between naltrexone- and methadone-treated individuals and found no significant differences. Methadone- and XR-naltrexone-treated participants exhibited 3.67% and 6.69% weight gain, respectively, from baseline to 6 months of treatment, but the change was non-significant. The study included a small sample size and may have been statistically underpowered [34].

Metabolic Signs: Lipid Profiles

According to folklore in some southern and central Asian countries, opioids are cardioprotective and prevent dyslipidemia [35]. The validity of such a belief was examined in several studies and covered in two reviews [35, 36]. A summary of currently available clinical findings on this question is presented in Table 2. In the largest cross-sectional study to date comprising 2239 individuals who use opioids, opioid use was significantly associated with lower levels of total (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol [37, 38]. The findings are consistent with some earlier studies, but others have yielded null results. Findings of antilipidemic effects of opioids should be interpreted with caution as a plethora of factors, such as dietary habits, physical activity, and concomitant drug use, may confound the effects of opioid use on lipid levels. It should be noted that in addition to the beneficial

Table 2 Lipid profiles in individuals who use opioids

Authors (year)	Study population	Underlying conditions	Comparison to individuals not using opioids			
			TG	TC	LDL	HDL
Kazemi et al. (2021)	2239 use opioids 7061 controls [37]	None	⇔	⇓	⇓	⇓
Sanli et al. (2015)	46 OUD 69 controls [40]	None	⇔	⇔	⇔	⇔
Gozashti et al. (2015)	53 OUD 55 controls [41]	None	⇔	⇓	NR	⇓
Masoomi et al. (2015)	103 OUD 114 controls [42]	None	⇔	⇔	NR	NR
Kouros et al. (2010)	77 OUD (35 heroin and 42 opium) 35 controls [43]	None	⇔	⇓	NR	NR
Asgary et al. (2008)	360 OUD 360 controls [44]	None	⇔	⇔	⇔	⇓
Javadi et al. (2014)	152 OUD 152 controls [45]	Admitted for acute myocardial infarction	⇔	⇔	⇔	⇔
Dehgani et al. (2013)	239 OUD 221 controls [46]	Admitted for acute myocardial infarction	⇓	⇔	⇔	⇔
Hoseini et al. (2019)	45 use opioids 135 controls	Diabetes	⇑	⇔	⇔	⇔
Rahimi et al. (2014)	179 OUD 195 controls [47]	Diabetes	⇔	⇔	⇔	⇓
Hosseini et al. (2011)	228 OUD 228 controls [48]	Diabetes	⇓	⇔	⇔	⇔
Azod et al. (2008)	23 OUD 46 controls [49]	Diabetes	⇔	⇔	⇔	⇔
Karam et al. (2004)	49 OUD 49 controls [50]	Diabetes	⇔	⇔	NR	⇓ (males)

LDL, low-density lipoprotein cholesterol; *HDL*, high-density lipoprotein cholesterol; *TG*, triglycerides; *TC*, total cholesterol; *NR*, not reported

cholesterol-lowering effects of opioids shown in some studies, opioid use has also been associated with a reduction in "good" HDL cholesterol levels. One study showed that total cholesterol and LDL levels were negatively correlated with opioid craving, although a causal relationship could not be inferred [39].

In a preclinical study, 10 days of methadone administration significantly decreased HDL and increased LDL cholesterol levels in both male and female rats, and decreased triglyceride levels in male rats [51]. A clinical study showed lower HDL levels in methadone-treated than buprenorphine-treated individuals. Additional analysis indicated that the duration of buprenorphine exposure was positively correlated with HDL levels, whereas the duration of methadone exposure was negatively correlated with HDL and positively correlated with triglyceride levels [16]. In contrast, a 6-month study of methadone treatment showed significantly increased serum triglyceride levels from baseline with no effect on cholesterol levels [52]. Despite the inconsistencies, these findings suggested dyslipidemia following methadone treatment. Further investigation of the relationships between medications for OUD and lipid profiles is warranted.

Metabolic Signs: Blood Pressure and Hypertension

Studies in healthy controls have shown vasodilation following a single intravenous injection of morphine [53, 54]. However, the long-term impact of chronic opioid use on blood pressure is unclear. One study found that OUD patients had significantly higher systolic blood pressure than non-OUD controls but no differences in diastolic blood pressure [47]. Another study demonstrated an increased prevalence of hypertension among individuals who use opioids than those who do not [17]. Despite significant findings, both studies were limited by not controlling for potential baseline differences in known factors associated with blood pressure, such as sex, age, body weight, and cigarette smoking [55]. A study that matched individuals who use versus never used opioids on age,

sex, and smoking status showed no significant difference in blood pressure but found greater severity of coronary atherosclerosis in individuals who use opioids as assessed with Gensini score and extent score [48]. Other studies showed no differences in blood pressure between individuals based on an OUD diagnosis [56, 57], and one showed that opioid use reduced the severity of myocardial infarction [46, 58]. Much of the extant studies associating opioid use with cardiac outcomes were conducted in India or Iran and, in some studies, the opioid used included non-pharmaceutical opioid formulations (e.g., crude opium [Teriak] and opium sap [Shireh]). Differences in the type, route of administration (i.e., oral, smoking, or intravenous injection), dosage, and duration of opioid use likely contributed to the inconsistent study findings [50]. Furthermore, there is a paucity of literature on the effects of medications for OUD. Therefore, studies are needed to establish the effects of opioids on blood pressure and hypertension [59].

Metabolic Signs: Glucose Metabolism

Both endogenous and exogenous opioids alter glucose metabolism in clinical and preclinical models [60, 61]. The glucose-altering effects of opioids are dependent upon baseline glucose levels. Seminal papers dating back to the 1980s reported hyperglycemia in individuals with OUD [62, 63], similar to individuals with non-insulin-dependent diabetes mellitus [64]. However, opioids appear to have hypoglycemic effects in individuals with baseline hyperglycemia, such as diabetes mellitus [65] (Table 3).

Altered secretion of glucoregulatory hormones may mediate the glycemic effects of opioids. The pancreas, the major endocrine organ that regulates glucose levels through secretion of insulin and glucagon, expresses opioid receptors [69]. Individuals with OUD show impaired insulin sensitivity. Individuals with OUD exhibited higher fasting levels of insulin and glucagon than age-, sex-,

Table 3 Glucose metabolism in individuals who use opioids

Authors (year)	Study population	Underlying conditions	Comparison to individuals not using opioids		
			FBG	HbA1c	Insulin
Hoseini et al. (2019)	45 use opioids 135 controls [66]	Type 2 diabetes	⇔	⇔	NR
Rahimi et al. (2014)	179 OUD 195 controls [47]	Type 2 diabetes	⇔	⇔	NR
Hosseini et al. (2011)	228 OUD 228 controls [48]	Type 2 diabetes	⇔	NR	NR
Azod et al. (2008)	23 OUD 46 controls [49]	Type 2 diabetes	⇓	⇔	NR
Karam et al. (2004)	49 OUD 49 controls [50]	Type 2 diabetes	⇔	⇓ (males)	NR
Gozashti et al. (2015)	53 OUD 55 controls [41]	None	⇑	⇔	⇓
Sanli et al. (2015)	46 OUD 69 controls [40]	None	⇔	NR	NR
Masoomi et al. (2015)	103 OUD 114 controls [42]	None	⇔	NR	NR
Pereska et al. (2012)	78 OUD 32 controls [67]	None	⇔	NR	⇑[A]
Kouros et al. (2010)	42 OUD 35 controls [43]		⇓	NR	NR
Ceriello et al. (1987)	30 OUD (15 heroin and 15 methadone) 15 controls [63]	None	⇑[B]	NR	⇑[C]
Passarielle et al. (1983)	15 OUD 15 controls [62]	None	⇔	NR	⇑
Vescovi et al. (1982)	10 OUD on methadone 10 controls [68]	None	⇔	NR	⇑[C]

[A]Insulin resistance assessed using a homeostatic model assessment of insulin resistance

[B]During oral glucose tolerance test

[C]Higher fasting insulin but lower insulin following glucose stimulation

FBG, fasting blood glucose; *HbA1c*, hemoglobin A1c; *NR*, not reported

and weight-matched control participants. Furthermore, OUD individuals exhibited a blunted and delayed insulin response to an intravenous glucose load [62, 63] but normal insulin responses to arginine, similar to the dysfunctional pattern of pancreatic beta cell activity in non-insulin-dependent diabetes mellitus [70]. There are variable findings in comparisons between glucose levels in individuals with OUD and controls, with some studies showing no difference in blood glucose levels [40, 42, 67] and others showing elevated glucose at fasting or in response to oral/intravenous glucose stimulation [41, 63]. In one study, the rate of glucose utilization in the OUD group fell to the diabetic range (OUD vs. control: $K_G = 0.96 \pm 0.09\%$/min vs. $1.65 \pm 0.10\%$/min) [62].

A rodent study showed that daily methadone administration over a 35-day period increased resting serum glucose [51, 71] and impaired oral glucose tolerance (i.e., higher levels of serum glucose after administration of an oral glucose load) [58]. The rats also demonstrated impairments in key enzymes related to glucose metabolism (i.e., diminished glycolytic activity of hexokinase and phosphofructokinase-1), resulting in a higher plasma glucose concentration [71]. This was accompanied by greater gluconeogenic activity of glucose-6-phosphatase and fructose-1,6-biphosphatase, augmenting the production of plasma glucose [71]. These findings led the authors to conclude that methadone maintenance produces a metabolic state similar to non-insulin-dependent diabetes.

Disturbances in glucose metabolism have clinical implications for individuals with OUD who receive methadone treatment. In a prospective chart review study, 18% of methadone-maintained OUD individuals were diagnosed with diabetes mellitus, nearly double the 9.6% prevalence in the general population [72]. The association between buprenorphine and glucose metabolism is less clear than that for methadone. In individuals undergoing hip replacement surgery, 0.3 mg buprenorphine was injected intravenously during the induction of anesthesia. Then, 0.4 mg was administered sublingually during the postoperative period, approximately 3 h after the first dose. Blood glucose increased following the intravenous dose but decreased at 3 h following the second dose of buprenorphine [73]. Thus, buprenorphine may increase glucose concentration at low initial doses but depress them at higher or subsequent doses [64].

Mechanisms of Action

Elucidating the mechanistic pathways underlying opioid- and medications for OUD-associated metabolic differences is key for developing interventions to address these effects clinically.

(1) Alterations in Brain Reward Circuitry, Eating Behavior, and Taste Perception

Brain reward circuitry promotes the continued performance of a behavior following the pairing of the behavior with a pleasurable outcome [74]. Neutral audiovisual stimuli that repeatedly signal the arrival of reward can become conditioned stimuli (i.e., cues) and trigger conditioned responses that include reward seeking. As such, exposure to food cues increases craving for food, activates the reward circuitry in the brain that includes the basal ganglia and prefrontal cortex [75, 76], and contributes to eating and weight gain [77]. Chronic opioid exposure attenuates reward sensitivity [78]. Given the higher reward potency of drugs of abuse, patients with OUD showed heightened incentive motivation towards opioids [79] and reduced interest in naturally rewarding activities [80]. Rats with a history of heroin use showed reduced conditioned responses to food cues [81]. Compared to healthy controls, patients with OUD demonstrated lower prefrontal neural activity in response to food cues [82, 83]. Preference for opioids in lieu of food constitutes one possible mechanistic pathway underlying weight loss in OUD individuals [78].

Seemingly in contrast with a preference for opioids in lieu of foods, individuals with OUD maintained on opioid agonists or when abstinent demonstrated increased preference and consumption of foods with high-sugar contents [84–86], with added sugar contributing ~ 30% of total caloric intake [87]. Cerebral mu-opioid receptors (MORs) are targets of medications for OUD, and they modulate eating behavior and taste perception [88]. In rodents, genetic knockout of MOR decreased sucrose licking and the effects were enhanced in response to the noncaloric sweetener sucralose, implicating MORs in the hedonic or pleasurable aspect of feeding, as opposed to having a homeostatic effect [89]. Individuals with OUD maintained on MOR agonists methadone or buprenorphine displayed higher sweet taste thresholds than healthy controls, whereas MOR antagonism by naltrexone reversed the sweet taste threshold to control levels [90]. In drug-naïve rodents, methadone administration significantly increased caloric intake from high fructose corn syrup consumption at the expense of chow consumption, ultimately leading to weight loss [91]. Several clinical studies have reported similar aberrations in the dietary habits of methadone or buprenorphine patients, including greater consumption of unhealthy junk foods, especially those high in sugar, with associated weight gain [64, 86, 92]. Based on self-report, individuals on methadone add significantly more sugar to caffeinated beverages than healthy control subjects [93]. However, in contrast to these findings, other studies have shown no significant differences in sweetness preference, liking, or desire between patients on buprenorphine and methadone, OUD individual in recovery, and healthy controls [93, 94]. Opioid antagonists including the MOR antagonist GSK1521498 reduced

hedonic rating for sweetened dairy products [95]. Likewise, one injection of long-acting extended-release MOR antagonist naltrexone in individuals with OUD significantly reduced sweet "liking" and "wanting" ratings [96]. MORs are also involved in taste perception and naltrexone reduced sweet taste perception in OUD individuals [90, 96]. Thus, the dual role of the MOR in hedonic feeding and taste perception may have implications for nutritional choices and metabolic health in individuals with OUD.

Decreased frequency of eating and poor nutrient absorption contribute to weight loss in individuals with OUD [23, 87, 97]. Opioid receptors (mu-, delta-, and kappa-) are expressed throughout the gastrointestinal tract, and opioid use is linked to a plethora of gastrointestinal effects such as constipation, nausea, abdominal pain, and gas, collectively known as opioid-induced bowel dysfunction (OIBD) [98]. Morphine slowed gastrointestinal transit time in rats, as evidenced by an increased latency for Evans blue dye to appear in fecal matter and reduced colonic migrating motor contractions [99]. Gastrointestinal discomfort experienced by individuals using opioids may deter eating and contribute to weight loss. Socioeconomic status may also contribute to altered feeding behavior. Due to the high costs of maintaining drug use and difficulty in maintaining stable employment, individuals with OUD are more likely than healthy individuals to experience homelessness/housing instability and be financially limited [100]. In a cross-sectional questionnaire study conducted at a needle exchange program, only 5.6% of the participants were employed and 51% reported having slept outdoors in the last 6 months. A majority (54.4%) of the participants also reported having not eaten enough due to a lack of money [101].

(2) Hormonal Changes

Hormonal changes are another possible mechanistic pathway through which opioids dysregulate metabolism.

Adiponectin

Adiponectin is a hormone secreted from adipocytes that prevents cardiac dysfunction and impairments in glucose and lipid metabolism [102]. Several studies have linked serum adiponectin levels to reduced risk of metabolic syndrome [103, 104]. Individuals using opioids had lower serum adiponectin levels than those who did not [52, 105, 106], which persisted even after adjusting for BMI, lipid levels, and the presence of type 2 diabetes and hypertension [105]. Adiponectin levels were not significantly altered by methadone administration and remained low in individuals following 6 months or 1 year of treatment [52, 106]. Therefore, decreased levels of cardioprotective adiponectin may contribute to dysregulated metabolic functioning.

Homocysteine

Homocysteine is a sulfur-containing amino acid formed from the breakdown of protein. Enzymes implicated in homocysteine metabolism require vitamins B_{12} and folate as cofactors. Elevated homocysteine metabolism was seen in OUD individuals, likely attributable to poorer nutritional status [42, 107]. Several large-scale epidemiological studies associated elevated homocysteine levels with elevated blood pressure and risk of hypertension [108, 109]. Proposed mechanisms for these effects include lower availability of the vasodilator nitric oxide, greater oxidative stress, and damage to the endothelial lining of vascular tissues [110]. Studies also demonstrate strong evidence of an association of high homocysteine levels with insulin resistance and poor glucose metabolism [111, 112]

Hypothalamic–Pituitary–Adrenal Axis Hormones

The hypothalamic–pituitary–adrenal axis (HPA) is an important stress response system that consists of the sequential secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH) from the anterior pituitary, and cortisol from the adrenal cortex [113]. The role of cortisol in regulating body weight and metabolism is supported by reduced and elevated body weights in individuals with pathological states of hypocortisolism (Addison disease) and hypercortisolism (Cushing's syndrome), respectively [114]. In healthy individuals, morning salivary cortisol levels were positively correlated with BMI, waist/hip circumference ratio, and abdominal sagittal diameter [115]. Cortisol may stimulate feeding, especially "stress eating." One study differentiated women as high or low cortisol reactors and found greater caloric consumption following laboratory-induced stress in high cortisol reactors. Further examination of food choices demonstrated greater preferences for high-fat sweet foods in high cortisol reactors [116].

In patients receiving opioid analgesic therapy, approximately 9% experienced opioid-induced adrenal insufficiency (OIAI), in which the adrenal glands produce an insufficient amount of cortisol [117]. While OIAI is an extreme aberration in adrenal function associated with opioid use, reduced urinary and blood cortisol levels of a less extreme nature have been observed with opioid administration [118–120]. In contrast, OUD individuals undergoing treatment with methadone had elevated hair cortisol levels [121] and increased blood cortisol in response to yohimbine challenge compared to healthy controls [122]. Elevated cortisol levels may constitute one mechanism through which opioid use and medications for OUD alter body weights. However, findings of altered cortisol responses to opioids and methadone may be confounded by withdrawal-related stress [123] and the

stress/anxiety state of participants [121], so they should be interpreted with caution.

(3) Inflammation and Oxidative Stress

Oxidative stress is characterized by an imbalanced state of reactive oxygen species accumulation accompanied by insufficient antioxidant defense [124]. Various biomarkers of oxidative stress have been linked to metabolic signs [125]. Individuals with more metabolic signs had higher plasma levels of H_2O_2 and lipid peroxidation [125], markers of oxidative stress. Adiposity is a well-established risk factor for metabolic syndrome, and the pharmacological reduction of reactive oxygen species reversed impairments in glucose and lipid metabolism in rodents [126], further bolstering the role of oxidative stress in metabolic dysfunction.

The elicitation of oxidative stress following opioid exposure may contribute to metabolic dysfunction in individuals with OUD, particularly those with co-occurring HIV. In HIV-infected rhesus macaques, the induction of morphine dependence increased plasma levels of malondialdehyde and 8-isoprostanes, markers of lipid peroxidation, compared to non-morphine-dependent HIV monkeys [127]. Similar findings were obtained in mice, such that morphine increased mitochondrial reactive oxygen species in the spinal dorsal horn, an effect exacerbated by the injection of HIV glycoprotein gp120 [128]. One possible pathway implicated in morphine-associated oxidative stress is the reduction of antioxidant capacity, as demonstrated by lower activity of superoxide dismutase, catalase, and glutathione peroxidase in morphine-treated mice than in controls [129].

Conclusion

Although OUD is well studied, much of the research has focused on the neuropathophysiology of addiction and there is a paucity of literature on the metabolic effects of opioid use and recovery. Our understanding of metabolism in OUD individuals is further limited by wide inconsistencies in the literature, which may be attributable to a lack of differentiation between synthetic (e.g., fentanyl) and naturally derived (e.g., morphine) opioids. Moreover, individuals with OUD are more likely to experience socioeconomic hardship and poor health which may affect metabolic health and confound study results. Despite the existing limitations, in this review, we reported the effects of opioid use and MAT on each element of the metabolic syndrome and the risk of developing metabolic syndrome.

Opioid use was associated with lower body weight and adiposity and a better lipid profile than was seen in non-opioid-using controls. Interestingly, OUD impaired insulin sensitivity in individuals without underlying metabolic conditions but reduced blood glucose levels in those with diabetes mellitus. Data on the metabolic effects of agonists methadone and buprenorphine in recovering OUD patients are limited, but suggest the occurrence of weight gain, dyslipidemia, and hyperglycemia. Naltrexone decreases the liking and wanting of sweet food, which may have implications for protecting against metabolic impairing, but this remains to be further studied. Mechanisms underlying opioid-associated metabolic alterations require further elucidation. Eating behavior and nutritional status can be further modulated by the complex involvement of opioids in the gastrointestinal system. Although medications for OUD provide protection against a variety of psychosocial and health consequences, our review underscores the need to consider patients' long-term metabolic health and further research is needed to determine how best to reduce the risk of metabolic disorder in OUD patients using opioid agonist medications. Studies are also needed to elucidate the relationship between opioids and metabolism and identify factors (e.g., OUD severity and genetic disposition) that predispose individuals to greater metabolic alterations. A better understanding of these effects could improve treatment strategies and thereby enhance the long-term health of individuals with OUD.

Declarations

Conflict of Interest Dr. Kranzler is a member of advisory boards for Dicerna Pharmaceuticals, Sophrosyne Pharmaceuticals, Clearmind Medicine and Entheon Pharmaceuticals; a consultant to Sobrera Pharmaceuticals; the recipient of research funding and medication supplies for an investigator-initiated study from Alkermes; a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last 3 years by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, Otsuka, and Pear Therapeutics; and a holder of US patent 10,900,082 titled: "Genotype-guided dosing of opioid agonists," issued 26 January 2021. The other authors report no relevant financial interests. This work was supported by the following National Institutes of Health grants: AA026892 (Wiers), DA051709 (Shi), and DA046345 (Kranzler). Li is supported by the NIDA T32 Translational Addiction Research Fellowship Program (T32DA028874-11).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Centers for Disease Control and Prevention (CDC). Vital signs: overdoses of prescription opioid pain relievers and other drugs among women--United States, 1999-2010. MMWR Morb Mortal Wkly Rep. 2013;62(26):537–42.
2. Wilson N, Kariisa M, Seth P, Smith HT, Davis NL. Drug and opioid-involved overdose deaths - United States, 2017-2018. MMWR Morb Mortal Wkly Rep. 2020;69(11):290–7. https://doi.org/10.15585/mmwr.mm6911a4.

3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). 2013.
4. Rhee TG, Rosenheck RA. Association of current and past opioid use disorders with health-related quality of life and employment among US adults. Drug Alcohol Depend. 2019;199:122–8. https://doi.org/10.1016/j.drugalcdep.2019.03.004.
5. Nielsen S, Larance B, Degenhardt L, Gowing L, Kehler C, Lintzeris N. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database of Systematic Reviews. 2016(5):CD011117. https://doi.org/10.1002/14651858.CD011117.pub2
6. Ma J, Bao Y-P, Wang R-J, Su M-F, Liu M-X, Li J-Q, et al. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. Mol Psychiatry. 2019;24(12):1868–83. https://doi.org/10.1038/s41380-018-0094-5.
7. Mattoo SK, Chakraborty K, Basu D, Ghosh A, Vijaya Kumar KG, Kulhara P. Prevalence & correlates of metabolic syndrome in alcohol & opioid dependent inpatients. Indian J Med Res. 2011;134(3):341–8.
8. Kassi E, Pervanidou P, Kaltsas G, Chrousos G. Metabolic syndrome: definitions and controversies. BMC Med. 2011;9(1):48. https://doi.org/10.1186/1741-7015-9-48.
9. Singh Balhara YP, Jain R, Kuppili PP, Shukla A, Chawla N, Gupta R. Which criteria to use to identify metabolic syndrome among patients with addictive disorders?: observations among patients with alcohol and opioid dependence syndrome. Indian J Endocrinol Metab. 2018;22(4):565–8. https://doi.org/10.4103/ijem.IJEM_617_17.
10. Samson SL, Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am. 2014;43(1):1–23. https://doi.org/10.1016/j.ecl.2013.09.009.
11. Hall GC, Morant SV, Carroll D, Gabriel ZL, McQuay HJ. An observational descriptive study of the epidemiology and treatment of neuropathic pain in a UK general population. BMC Fam Pract. 2013;14:28. https://doi.org/10.1186/1471-2296-14-28.
12. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017;377(1):13–27. https://doi.org/10.1056/NEJMoa1614362.
13. McAuley PA, Blair SN. Obesity paradoxes. J Sports Sci. 2011;29(8):773–82. https://doi.org/10.1080/02640414.2011.553965.
14. Hunger JM, Major B. Weight stigma mediates the association between BMI and self-reported health. Health Psychol: Off J Div Health Psychol Am Psychol Assoc. 2015;34(2):172–5. https://doi.org/10.1037/hea0000106.
15. Major B, Tomiyama AJ, Hunger JM. The negative and bidirectional effects of weight stigma on health. In: Major B, Dovidio JF, Link BG, editors. The Oxford handbook of stigma, discrimination, and health. Oxford Library of Psychology; 2018. https://doi.org/10.1093/oxfordhb/9780190243470.013.27.
16. Elman I, Howard M, Borodovsky JT, Mysels D, Rott D, Borsook D, et al. Metabolic and addiction indices in patients on opioid agonist medication-assisted treatment: a comparison of buprenorphine and methadone. Sci Rep. 2020;10(1):5617. https://doi.org/10.1038/s41598-020-62556-0.
17. Yousefzadeh G, Shokoohi M, Najafipour H, Eslami M, Salehi F. Association between opium use and metabolic syndrome among an urban population in Southern Iran: results of the Kerman Coronary Artery Disease Risk Factor Study (KERCADRS). ARYA Atheroscler. 2015;11(1):14–20.
18. Vallecillo G, Robles MJ, Torrens M, Samos P, Roquer A, Martires PK, et al. Metabolic syndrome among individuals with heroin use disorders on methadone therapy: prevalence, characteristics, and related factors. Subst Abus. 2018;39(1):46–51. https://doi.org/10.1080/08897077.2017.1363122.
19. Gierach M, Gierach J, Ewertowska M, Arndt A, Junik R. Correlation between body mass index and waist circumference in patients with metabolic syndrome. ISRN Endocrinol. 2014;2014:514589. https://doi.org/10.1155/2014/514589.
20. Gutin I. In BMI we trust: reframing the body mass index as a measure of health. Soc Theory Health. 2018;16(3):256–71. https://doi.org/10.1057/s41285-017-0055-0.
21. Hu L, Matthews A, Shmueli-Blumberg D, Killeen TK, Tai B, VanVeldhuisen P. Prevalence of obesity for opioid- and stimulant-dependent participants in substance use treatment clinical trials. Drug Alcohol Depend. 2018;190:255–62. https://doi.org/10.1016/j.drugalcdep.2018.06.014.
22. McIlwraith F, Betts KS, Jenkinson R, Hickey S, Burns L, Alati R. Is low BMI associated with specific drug use among injecting drug users? Subst Use Misuse. 2014;49(4):374–82. https://doi.org/10.3109/10826084.2013.841246.
23. Nazrul Islam SK, Jahangir Hossain K, Ahmed A, Ahsan M. Nutritional status of drug addicts undergoing detoxification: prevalence of malnutrition and influence of illicit drugs and lifestyle. Br J Nutr. 2002;88(5):507–13. https://doi.org/10.1079/bjn2002702.
24. Tang AM, Forrester JE, Spiegelman D, Flanigan T, Dobs A, Skinner S, et al. Heavy injection drug use is associated with lower percent body fat in a multi-ethnic cohort of HIV-positive and HIV-negative drug users from three U. S. cities. Am J Drug Alcohol Abuse. 2010;36(1):78–86. https://doi.org/10.3109/00952990903544851.
25. Peles E, Schreiber S, Sason A, Adelson M. Risk factors for weight gain during methadone maintenance treatment. Subst Abus. 2016;37(4):613–8. https://doi.org/10.1080/08897077.2016.1179705.
26. Fenn JM, Laurent JS, Sigmon SC. Increases in body mass index following initiation of methadone treatment. J Subst Abuse Treat. 2015;51:59–63. https://doi.org/10.1016/j.jsat.2014.10.007.
27. Manza P, Kroll D, McPherson KL, Johnson A, Dennis E, Hu L, et al. Sex differences in weight gain during medication-based treatment for opioid use disorder: a meta-analysis and retrospective analysis of clinical trial data. Drug Alcohol Depend. 2022;238:109575. https://doi.org/10.1016/j.drugalcdep.2022.109575.
28. Sadek GE, Chiu S, Cernovsky ZZ. Body composition changes associated with methadone treatment. Int J High Risk Behav Addict. 2016;5(1):e27587. https://doi.org/10.5812/ijhrba.27587.
29. Baykara S, Alban K. The effects of buprenorphine/naloxone maintenance treatment on sexual dysfunction, sleep and weight in opioid use disorder patients. Psychiatry Res. 2019;272:450–3. https://doi.org/10.1016/j.psychres.2018.12.153.
30. Comer SD, Sullivan MA, Yu E, Rothenberg JL, Kleber HD, Kampman K, et al. Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. Arch Gen Psychiatry. 2006;63(2):210–8. https://doi.org/10.1001/archpsyc.63.2.210.
31 Li X, Bello NT. Anorectic state of obesity medications in the United States. Are leaner times ahead? Expert Opin Pharmacother. 2020;21(2):167–72. https://doi.org/10.1080/14656566.2019.1692815.
32. Malcolm R, O'Neil PM, Sexauer JD, Riddle FE, Currey HS, Counts C. A controlled trial of naltrexone in obese humans. Int J Obes. 1985;9(5):347–53.
33. Greenway FL, Dunayevich E, Tollefson G, Erickson J, Guttadauria M, Fujioka K, et al. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. J Clin Endocrinol Metab. 2009;94(12):4898–906. https://doi.org/10.1210/jc.2009-1350.

34. Mysels DJ, Vosburg SK, Benga I, Levin FR, Sullivan MA. Course of weight change during naltrexone versus methadone maintenance for opioid-dependent patients. J Opioid Manag. 2011;7(1):47–53. https://doi.org/10.5055/jom.2011.0048.
35. Masoudkabir F, Sarrafzadegan N, Eisenberg MJ. Effects of opium consumption on cardiometabolic diseases. Nat Rev Cardiol. 2013;10(12):733–40. https://doi.org/10.1038/nrcardio.2013.159.
36. Najafipour H, Beik A. The impact of opium consumption on blood glucose, serum lipids and blood pressure, and related mechanisms. Front Physiol. 2016;7. https://doi.org/10.3389/fphys.2016.00436.
37. Kazemi M, Bazyar M, Naghizadeh MM, Dehghan A, Rahimabadi MS, Chijan MR, et al. Lipid profile dysregulation in opium users based on Fasa PERSIAN cohort study results. Sci Rep. 2021;11(1):12058. https://doi.org/10.1038/s41598-021-91533-4.
38. Jamali Z, Noroozi Karimabad M, Khalili P, Sadeghi T, Sayadi A, Mohammadakbari Rostamabadi F, et al. Prevalence of dyslipidemia and its association with opium consumption in the Rafsanjan cohort study. Sci Rep. 2022;12(1):11504. https://doi.org/10.1038/s41598-022-13926-3.
39. Lin SH, Yang YK, Lee SY, Hsieh PC, Chen PS, Lu RB, et al. Association between cholesterol plasma levels and craving among heroin users. J Addict Med. 2012;6(4):287–91. https://doi.org/10.1097/ADM.0b013e318262a9a1.
40. Sanli DB, Bilici R, Suner O, Citak S, Kartkaya K, Mutlu FS. Effect of different psychoactive substances on serum biochemical parameters. Int J High Risk Behav Addict. 2015;4(2):e22702. https://doi.org/10.5812/ijhrba.22702.
41. Gozashti MH, Yazdi F, Salajegheh P, Dehesh MM, Divsalar K. Fasting blood glucose and insulin level in opium addict versus non-addict individuals. Addict Health. 2015;7(1–2):54–9.
42. Masoomi M, Azdaki N, Shahouzehi B. Elevated plasma homocysteine concentration in opium-addicted individuals. Addict Health. 2015;7(3–4):149–56.
43. Kouros D, Tahereh H, Mohammadreza A, Minoo MZ. Opium and heroin alter biochemical parameters of human's serum. Am J Drug Alcohol Abuse. 2010;36(3):135–9. https://doi.org/10.3109/00952991003734277.
44. Asgary S, Sarrafzadegan N, Naderi GA, Rozbehani R. Effect of opium addiction on new and traditional cardiovascular risk factors: do duration of addiction and route of administration matter? Lipids Health Dis. 2008;7:42. https://doi.org/10.1186/1476-511x-7-42.
45. Javadi HR, Allami A, Mohammadi N, Alauddin R. Opium dependency and in-hospital outcome of acute myocardial infarction. Med J Islam Repub Iran. 2014;28:122.
46. Dehghani F, Masoomi M, Haghdoost AA. Relation of opium addiction with the severity and extension of myocardial infarction and its related mortality. Addict Health. 2013;5(1–2):35–42.
47. Rahimi N, Gozashti MH, Najafipour H, Shokoohi M, Marefati H. Potential effect of opium consumption on controlling diabetes and some cardiovascular risk factors in diabetic patients. Addict Health. 2014;6(1–2):1–6.
48. Hosseini SK, Masoudkabir F, Vasheghani-Farahani A, Alipour-Parsa S, Sheikh Fathollahi M, Rahimi-Foroushani A, et al. Opium consumption and coronary atherosclerosis in diabetic patients: a propensity score-matched study. Planta Med. 2011;77(17):1870–5. https://doi.org/10.1055/s-0031-1280017.
49. Azod L, Rashidi M, Afkhami-Ardekani M, Kiani G, Khoshkam F. Effect of opium addiction on diabetes. Am J Drug Alcohol Abuse. 2008;34(4):383–8. https://doi.org/10.1080/00952990802122580.
50. Karam GA, Reisi M, Kaseb AA, Khaksari M, Mohammadi A, Mahmoodi M. Effects of opium addiction on some serum factors in addicts with non-insulin-dependent diabetes mellitus. Addict Biol. 2004;9(1):53–8. https://doi.org/10.1080/13556210410001674095.
51. Tahergorabi Z, Rahmani H, Williams J, Moodi M. The effect of methadone on blood glucose, lipids and glucose-modulating hormones in methadone-dependent Wistar rats. Toxicol Res. 2020;36(3):221–6. https://doi.org/10.1007/s43188-019-00019-z.
52. Montazerifar F, Karajibani M, Lashkaripour K, Yousefi M. Evaluation of serum adiponectin concentrations among drug abusers on methadone maintenance treatment. Int J High Risk Behav Addict. 2013;2(3):117–21. https://doi.org/10.5812/ijhrba.14021.
53. Afshari R, Maxwell SR, Webb DJ, Bateman DN. Morphine is an arteriolar vasodilator in man. Br J Clin Pharmacol. 2009;67(4):386–93. https://doi.org/10.1111/j.1365-2125.2009.03364.x.
54 Zelis R, Mansour EJ, Capone RJ, Mason DT. The cardiovascular effects of morphine. The peripheral capacitance and resistance vessels in human subjects. J Clin Invest. 1974;54(6):1247–58. https://doi.org/10.1172/jci107869.
55. Wang W, Lee ET, Fabsitz RR, Devereux R, Best L, Welty TK, et al. A longitudinal study of hypertension risk factors and their relation to cardiovascular disease: the Strong Heart Study. Hypertension. 2006;47(3):403–9. https://doi.org/10.1161/01.Hyp.0000200710.29498.80.
56. Najafi M, Sheikhvatan M. Plausible impact of dietary habits on reduced blood sugar in diabetic opium addicts with coronary artery disease. Int Cardiovasc Res J. 2012;6(3):75–8.
57. Najafi M, Sheikhvatan M. Does analgesic effect of opium hamper the adverse effects of severe coronary artery disease on quality of life in addicted patients? Anesth Pain Med. 2012;2(1):22–7. https://doi.org/10.5812/aapm.5139.
58. Fallahzadeh MA, Salehi A, Naghshvarian M, Fallahzadeh MH, Poustchi H, Sepanlou SG, et al. Epidemiologic study of opium use in Pars Cohort Study: a study of 9000 adults in a rural southern area of Iran. Arch Iran Med. 2017;20(4):205–10.
59 Feuerstein G, Siren AL. The opioid peptides. A role in hypertension? Hypertension. 1987;9(6):561–5. https://doi.org/10.1161/01.hyp.9.6.561.
60. Feldberg W, Shaligram SV. The hyperglycaemic effect of morphine. Br J Pharmacol. 1972;46(4):602–18. https://doi.org/10.1111/j.1476-5381.1972.tb06887.x.
61. Koekkoek LL, van der Gun LL, Serlie MJ, la Fleur SE. The clash of two epidemics: the relationship between opioids and glucose metabolism. Curr Diab Rep. 2022. https://doi.org/10.1007/s11892-022-01473-0.
62 Passariello N, Giugliano D, Quatraro A, Consoli G, Sgambato S, Torella R, et al. Glucose tolerance and hormonal responses in heroin addicts. A possible role for endogenous opiates in the pathogenesis of non-insulin-dependent diabetes. Metabolism. 1983;32(12):1163–5. https://doi.org/10.1016/0026-0495(83)90065-3.
63. Ceriello A, Giugliano D, Passariello N, Quatraro A, Dello Russo P, Torella R, et al. Impaired glucose metabolism in heroin and methadone users. Horm Metab Res. 1987;19(9):430–3. https://doi.org/10.1055/s-2007-1011844.
64. Mysels DJ, Sullivan MA. The relationship between opioid and sugar intake: review of evidence and clinical applications. J Opioid Manag. 2010;6(6):445–52. https://doi.org/10.5055/jom.2010.0043.
65. Chrétien B, Dolladille C, Hamel-Sénécal L, Sassier M, Faillie JL, Miremont-Salamé G, et al. Comparative study of hypoglycaemia induced by opioids. Is it a class effect? Expert Opin Drug Saf. 2019;18(10):987–92. https://doi.org/10.1080/14740338.2019.1646246.
66. Hoseini SS, Saadatjoo SA, Nakhaee S, Amirabadizadeh A, Rezaie M, Mehrpour O. Potential effect of opium addiction on lipid profile and blood glucose concentration in type 2 diabetic

patients in Iran. Journal of Substance Use. 2019;24(4):420–5. https://doi.org/10.1080/14659891.2019.1588404.
67. Pereska Z, Bozinovska C, Dimitrovski C, Cakalarovski K, Chibishev A, Zdravkovska M, et al. Heroin dependence duration influences the metabolic parameters: mechanisms and consequences of impaired insulin sensitivity in hepatitis C virus seronegative heroin dependents. J Addict Med. 2012;6(4):304–10. https://doi.org/10.1097/ADM.0b013e31826bd76c.
68. Vescovi PP, Pezzarossa A, Caccavari R, Valenti G, Butturini U. Glucose tolerance in opiate addicts. Diabetologia. 1982;23(5):459. https://doi.org/10.1007/bf00260963.
69. Peng J, Sarkar S, Chang SL. Opioid receptor expression in human brain and peripheral tissues using absolute quantitative real-time RT-PCR. Drug Alcohol Depend. 2012;124(3):223–8. https://doi.org/10.1016/j.drugalcdep.2012.01.013.
70. Giugliano D. Morphine, opioid peptides, and pancreatic islet function. Diabetes Care. 1984;7(1):92–8. https://doi.org/10.2337/diacare.7.1.92.
71. Sadava D, Alonso D, Hong H, Pettit-Barrett DP. Effect of methadone addiction on glucose metabolism in rats. Gen Pharmacol. 1997;28(1):27–9. https://doi.org/10.1016/s0306-3623(96)00165-6.
72. Fareed A, Casarella J, Amar R, Vayalapalli S, Drexler K. Benefits of retention in methadone maintenance and chronic medical conditions as risk factors for premature death among older heroin addicts. J Psychiatr Pract. 2009;15(3):227–34. https://doi.org/10.1097/01.pra.0000351884.83377.e2.
73. Bullingham RE, McQuay HJ, Dwyer D, Allen MC, Moore RA. Sublingual buprenorphine used postoperatively: clinical observations and preliminary pharmacokinetic analysis. Br J Clin Pharmacol. 1981;12(2):117–22. https://doi.org/10.1111/j.1365-2125.1981.tb01189.x.
74. Darvas M, Wunsch AM, Gibbs JT, Palmiter RD. Dopamine dependency for acquisition and performance of Pavlovian conditioned response. Proc Natl Acad Sci U S A. 2014;111(7):2764–9. https://doi.org/10.1073/pnas.1400332111.
75. Tang DW, Fellows LK, Small DM, Dagher A. Food and drug cues activate similar brain regions: a meta-analysis of functional MRI studies. Physiol Behav. 2012;106(3):317–24. https://doi.org/10.1016/j.physbeh.2012.03.009.
76. Noori HR, Cosa Linan A, Spanagel R. Largely overlapping neuronal substrates of reactivity to drug, gambling, food and sexual cues: a comprehensive meta-analysis. Eur Neuropsychopharmacol. 2016;26(9):1419–30. https://doi.org/10.1016/j.euroneuro.2016.06.013.
77. Boswell RG, Kober H. Food cue reactivity and craving predict eating and weight gain: a meta-analytic review. Obes Rev. 2016;17(2):159–77. https://doi.org/10.1111/obr.12354.
78. Volkow ND, Fowler JS, Wang GJ, Swanson JM, Telang F. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. Arch Neurol. 2007;64(11):1575–9. https://doi.org/10.1001/archneur.64.11.1575.
79. Shi Z, Jagannathan K, Padley JH, Wang AL, Fairchild VP, O'Brien CP, et al. The role of withdrawal in mesocorticolimbic drug cue reactivity in opioid use disorder. Addict Biol. 2021;26(4):e12977. https://doi.org/10.1111/adb.12977.
80. Kiluk BD, Yip SW, DeVito EE, Carroll KM, Sofuoglu M. Anhedonia as a key clinical feature in the maintenance and treatment of opioid use disorder. Clin Psychol Sci. 2019;7(6):1190–206. https://doi.org/10.1177/2167702619855659.
81. Crummy EA, Donckels EA, Baskin BM, Bentzley BS, Ferguson SM. The impact of cocaine and heroin drug history on motivation and cue sensitivity in a rat model of polydrug abuse. Psychopharmacology. 2020;237(1):55–68. https://doi.org/10.1007/s00213-019-05349-2.
82. Huhn AS, Brooner RK, Sweeney MM, Antoine D, Hammond AS, Ayaz H, et al. The association of prefrontal cortex response during a natural reward cue-reactivity paradigm, anhedonia, and demoralization in persons maintained on methadone. Addict Behav. 2021;113:106673. https://doi.org/10.1016/j.addbeh.2020.106673.
83. Huhn AS, Meyer RE, Harris JD, Ayaz H, Deneke E, Stankoski DM, et al. Evidence of anhedonia and differential reward processing in prefrontal cortex among post-withdrawal patients with prescription opiate dependence. Brain Res Bull. 2016;123:102–9. https://doi.org/10.1016/j.brainresbull.2015.12.004.
84. Kolarzyk E, Jenner B, Szpanowska-Wohn A, Pach D, Szurkowska M. The changes in taste preferences during 4 years period of methadone maintenance treatment. Przegl Lek. 2005;62(6):378–81.
85. Morabia A, Fabre J, Chee E, Zeger S, Orsat E, Robert A. Diet and opiate addiction: a quantitative assessment of the diet of non-institutionalized opiate addicts. Br J Addict. 1989;84(2):173–80. https://doi.org/10.1111/j.1360-0443.1989.tb00566.x.
86. Nolan LJ, Scagnelli LM. Preference for sweet foods and higher body mass index in patients being treated in long-term methadone maintenance. Subst Use Misuse. 2007;42(10):1555–66. https://doi.org/10.1080/10826080701517727.
87. Saeland M, Haugen M, Eriksen FL, Wandel M, Smehaugen A, Böhmer T, et al. High sugar consumption and poor nutrient intake among drug addicts in Oslo. Norway Br J Nutr. 2011;105(4):618–24. https://doi.org/10.1017/s000711451000397 1.
88. Kantonen T, Karjalainen T, Pekkarinen L, Isojärvi J, Kalliokoski K, Kaasinen V, et al. Cerebral μ-opioid and CB(1) receptor systems have distinct roles in human feeding behavior. Transl Psychiatry. 2021;11(1):442. https://doi.org/10.1038/s41398-021-01559-5.
89. Ostlund SB, Kosheleff A, Maidment NT, Murphy NP. Decreased consumption of sweet fluids in μ opioid receptor knockout mice: a microstructural analysis of licking behavior. Psychopharmacology. 2013;229(1):105–13. https://doi.org/10.1007/s00213-013-3077-x.
90. Green A, Kaul A, O'Shea J, Sharma E, Bennett L, Mullings EL, et al. Opiate agonists and antagonists modulate taste perception in opiate-maintained and recently detoxified subjects. J Psychopharmacol. 2013;27(3):265–75. https://doi.org/10.1177/0269881112472567.
91. Daniels S, Pratt M, Zhou Y, Leri F. Effect of steady-state methadone on high fructose corn syrup consumption in rats. J Psychopharmacol. 2018;32(2):215–22. https://doi.org/10.1177/0269881117742116.
92. Ochalek TA, Laurent J, Badger GJ, Sigmon SC. Sucrose subjective response and eating behaviors among individuals with opioid use disorder. Drug Alcohol Depend. 2021;227:109017. https://doi.org/10.1016/j.drugalcdep.2021.109017.
93. Bogucka-Bonikowska A, Baran-Furga H, Chmielewska K, Habrat B, Scinska A, Kukwa A, et al. Taste function in methadone-maintained opioid-dependent men. Drug Alcohol Depend. 2002;68(1):113–7. https://doi.org/10.1016/s0376-8716(02)00186-2.
94. Garfield JBB, Lubman DI. Associations between opioid dependence and sweet taste preference. Psychopharmacology. 2021;238(6):1473–84. https://doi.org/10.1007/s00213-021-05774-2.
95. Ziauddeen H, Chamberlain SR, Nathan PJ, Koch A, Maltby K, Bush M, et al. Effects of the mu-opioid receptor antagonist GSK1521498 on hedonic and consummatory eating behaviour: a proof of mechanism study in binge-eating obese subjects. Mol Psychiatry. 2013;18(12):1287–93. https://doi.org/10.1038/mp.2012.154.

96. Langleben DD, Busch EL, O'Brien CP, Elman I. Depot naltrexone decreases rewarding properties of sugar in patients with opioid dependence. Psychopharmacology. 2012;220(3):559–64. https://doi.org/10.1007/s00213-011-2503-1.
97. Sason A, Adelson M, Herzman-Harari S, Peles E. Knowledge about nutrition, eating habits and weight reduction intervention among methadone maintenance treatment patients. J Subst Abuse Treat. 2018;86:52–9. https://doi.org/10.1016/j.jsat.2017.12.008.
98. Szigethy E, Knisely M, Drossman D. Opioid misuse in gastroenterology and non-opioid management of abdominal pain. Nat Rev Gastroenterol Hepatol. 2018;15(3):168–80. https://doi.org/10.1038/nrgastro.2017.141.
99. Beckett EAH, Staikopoulos V, Hutchinson MR. Differential effect of morphine on gastrointestinal transit, colonic contractions and nerve-evoked relaxations in Toll-Like Receptor deficient mice. Sci Rep. 2018;8(1):5923. https://doi.org/10.1038/s41598-018-23717-4.
100. Chavez MN, Rigg KK. Nutritional implications of opioid use disorder: a guide for drug treatment providers. Psychol Addict Behav. 2020;34(6):699–707. https://doi.org/10.1037/adb0000575.
101. Strike C, Rudzinski K, Patterson J, Millson M. Frequent food insecurity among injection drug users: correlates and concerns. BMC Public Health. 2012;12:1058. https://doi.org/10.1186/1471-2458-12-1058.
102. Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol. 2004;24(1):29–33. https://doi.org/10.1161/01.Atv.0000099786.99623.Ef.
103. Gavrila A, Chan JL, Yiannakouris N, Kontogianni M, Miller LC, Orlova C, et al. Serum adiponectin levels are inversely associated with overall and central fat distribution but are not directly regulated by acute fasting or leptin administration in humans: cross-sectional and interventional studies. J Clin Endocrinol Metab. 2003;88(10):4823–31. https://doi.org/10.1210/jc.2003-030214.
104. Lee KW, Shin D. Prospective associations of serum adiponectin, leptin, and leptin-adiponectin ratio with incidence of metabolic syndrome: the Korean Genome and Epidemiology Study. Int J Environ Res Public Health. 2020;17(9). https://doi.org/10.3390/ijerph17093287
105. Shahouzehi B, Shokoohi M, Najafipour H. The effect of opium addiction on serum adiponectin and leptin levels in male subjects: a case control study from Kerman Coronary Artery Disease Risk Factors Study (KERCADRS). Excli j. 2013;12:916–23.
106. Housová J, Wilczek H, Haluzík MM, Kremen J, Krízová J, Haluzík M. Adipocyte-derived hormones in heroin addicts: the influence of methadone maintenance treatment. Physiol Res. 2005;54(1):73–8.
107. Tomedi LE, Bogen DL, Hanusa BH, Wisner KL, Bodnar LM. A pilot study of the nutritional status of opiate-using pregnant women on methadone maintenance therapy. Subst Use Misuse. 2012;47(3):286–95. https://doi.org/10.3109/10826084.2011.635324.
108. Lim U, Cassano PA. Homocysteine and blood pressure in the Third National Health and Nutrition Examination Survey, 1988–1994. Am J Epidemiol. 2002;156(12):1105–13. https://doi.org/10.1093/aje/kwf157.
109. Wang Y, Chen S, Yao T, Li D, Wang Y, Li Y, et al. Homocysteine as a risk factor for hypertension: a 2-year follow-up study. PLoS One. 2014;9(10):e108223. https://doi.org/10.1371/journal.pone.0108223.
110. Rodrigo R, Passalacqua W, Araya J, Orellana M, Rivera G. Homocysteine and essential hypertension. J Clin Pharmacol. 2003;43(12):1299–306. https://doi.org/10.1177/0091270003258190.
111. Deng M, Zhou J, Tang Z, Xiang J, Yi J, Peng Y, et al. The correlation between plasma total homocysteine level and gestational diabetes mellitus in a Chinese Han population. Sci Rep. 2020;10(1):18679. https://doi.org/10.1038/s41598-020-75797-w.
112. Meigs JB, Jacques PF, Selhub J, Singer DE, Nathan DM, Rifai N, et al. Fasting plasma homocysteine levels in the insulin resistance syndrome: the Framingham Offspring Study. Diabetes Care. 2001;24(8):1403–10. https://doi.org/10.2337/diacare.24.8.1403.
113. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53(4):865–71. https://doi.org/10.1016/s0022-3999(02)00429-4.
114. Dallman MF, la Fleur SE, Pecoraro NC, Gomez F, Houshyar H, Akana SF. Minireview: glucocorticoids–food intake, abdominal obesity, and wealthy nations in 2004. Endocrinology. 2004;145(6):2633–8. https://doi.org/10.1210/en.2004-0037.
115. Wallerius S, Rosmond R, Ljung T, Holm G, Björntorp P. Rise in morning saliva cortisol is associated with abdominal obesity in men: a preliminary report. J Endocrinol Invest. 2003;26(7):616–9. https://doi.org/10.1007/bf03347017.
116. Epel E, Lapidus R, McEwen B, Brownell K. Stress may add bite to appetite in women: a laboratory study of stress-induced cortisol and eating behavior. Psychoneuroendocrinology. 2001;26(1):37–49. https://doi.org/10.1016/s0306-4530(00)00035-4.
117. Li T, Cunningham JL, Gilliam WP, Loukianova L, Donegan DM, Bancos I. Prevalence of opioid-induced adrenal insufficiency in patients taking chronic opioids. J Clin Endocrinol Metab. 2020;105(10):e3766–75. https://doi.org/10.1210/clinem/dgaa499.
118. Abs R, Verhelst J, Maeyaert J, Van Buyten J-P, Opsomer F, Adriaensen H, et al. Endocrine consequences of long-term intrathecal administration of opioids. J Clin Endocrinol Metab. 2000;85(6):2215–22. https://doi.org/10.1210/jcem.85.6.6615.
119. Aloisi AM, Aurilio C, Bachiocco V, Biasi G, Fiorenzani P, Pace MC, et al. Endocrine consequences of opioid therapy. Psychoneuroendocrinology. 2009;34(Suppl 1):S162–8. https://doi.org/10.1016/j.psyneuen.2009.05.013.
120. Aloisi AM, Buonocore M, Merlo L, Galandra C, Sotgiu A, Bacchella L, et al. Chronic pain therapy and hypothalamic-pituitary-adrenal axis impairment. Psychoneuroendocrinology. 2011;36(7):1032–9. https://doi.org/10.1016/j.psyneuen.2010.12.017.
121. Yang J, Li J, Xu G, Zhang J, Chen Z, Lu Z, et al. Elevated hair cortisol levels among heroin addicts on current methadone maintenance compared to controls. PLoS One. 2016;11(3):e0150729. https://doi.org/10.1371/journal.pone.0150729.
122. Stine SM, Grillon CG, Morgan CA 3rd, Kosten TR, Charney DS, Krystal JH. Methadone patients exhibit increased startle and cortisol response after intravenous yohimbine. Psychopharmacology. 2001;154(3):274–81. https://doi.org/10.1007/s002130000644.
123. Bearn J, Buntwal N, Papadopoulos A, Checkley S. Salivary cortisol during opiate dependence and withdrawal. Addict Biol. 2001;6(2):157–62. https://doi.org/10.1080/13556210020040235.
124 Betteridge DJ. What is oxidative stress? Metabolism. 2000;49(2, Supplement 1):3–8. https://doi.org/10.1016/S0026-0495(00)80077-3.
125 Yubero-Serrano EM, Delgado-Lista J, Peña-Orihuela P, Perez-Martinez P, Fuentes F, Marin C, et al. Oxidative stress is associated with the number of components of metabolic syndrome: LIPGENE study. Exp Mol Med. 2013;45(6):e28-e. https://doi.org/10.1038/emm.2013.53.
126. Furukawa S, Fujita T, Shimabukuro M, Iwaki M, Yamada Y, Nakajima Y, et al. Increased oxidative stress in

obesity and its impact on metabolic syndrome. J Clin Invest. 2004;114(12):1752–61. https://doi.org/10.1172/jci21625.
127. Pérez-Casanova A, Husain K, Noel RJ, Rivera-Amill V, Kumar A. Interaction of SIV/SHIV infection and morphine on plasma oxidant/antioxidant balance in macaque. Mol Cell Biochem. 2008;308(1):169–75. https://doi.org/10.1007/s11010-007-9625-0.
128. Shi Y, Yuan S, Tang S-J. Reactive oxygen species (ROS) are critical for morphine exacerbation of HIV-1 gp120-induced pain. J Neuroimmune Pharmacol. 2021;16(3):581–91. https://doi.org/10.1007/s11481-020-09951-6.
129. Zhang YT, Zheng QS, Pan J, Zheng RL. Oxidative damage of biomolecules in mouse liver induced by morphine and protected by antioxidants. Basic Clin Pharmacol Toxicol. 2004;95(2):53–8. https://doi.org/10.1111/j.1742-7843.2004.950202.x.