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Determination of thallium in urine, blood, and hair in illicit opioid users in Iran

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Abstract

Context: Heavy metals, including thallium and lead, are introduced to illicit drug users' body as a result of using drugs such as cocaine and heroin.

Objective: This study aimed to determine urine, blood, and hair thallium (Tl) concentrations in illicit opioid users along with the relevant clinical signs and symptoms consistent with thallotoxicosis and to compare them with the corresponding variables in the control non-opioid user group.

Materials and Methods: This case–control study was conducted on 50 illicit opioid users who had abused opioids continuously for more than a year, referred to Amirie Drug Abuse Treatment Clinic in Kashan, Iran. The control group included 50 non-opioid users. Thallium concentrations in urine, blood, and hair were assessed in both groups ($n = 100$) using electrothermal (graphite furnace) atomic absorption spectrometry (ET AAS, GF AAS).

Results: In the studied group, the median (interquartile range) concentrations of thallium in urine, blood, and hair were 54.8 $\pm$ 79.9 μg/L, 14.5 $\pm$ 11.1 μg/L, and 5.4 $\pm$ 3.7 μg/g, respectively; these values were 4.8 $\pm$ 5.2 μg/L, 2.5 $\pm$ 2.4 μg/L, and 1.4 $\pm$ 1.1 μg/g, respectively, in the control group. There were significant differences in urine, blood, and hair thallium concentrations between the study group and the control group ($p < 0.001$). There were significant correlations between duration of illicit opioid use and urine thallium concentrations ($r = 0.394$, $p = 0.005$) and hair thallium concentrations ($r = 0.293$, $p = 0.039$), but not with blood thallium concentrations ($r = 0.246$, $p = 0.085$). Urine and blood thallium concentrations of illicit opioid users with clinical signs and symptoms consistent with thallotoxicosis of weakness ($p = 0.01$), depression ($p = 0.03$), and headache ($p = 0.03$) were higher than users without these problems.

Discussion and conclusion: The results of the study showed that thallium concentrations in urine, blood, and hair in illicit opioid users were significantly higher than the comparable concentrations in the control group. This can be due to the use of illicit opioids adulterated with thallium. Also, this study showed long-term illicit opioid use may lead to thallium exposure. In addition, cigarette smoking was associated with increased thallium exposure.

Keywords

Thallium, opioid users, urine, blood, hair, thallotoxicosis

Introduction

Opioid use disorder is an important health hazard and clinical problem around the world. Iran appears to play an important transit role in the transfer of narcotics from Afghanistan to the other countries.[1,2] Reports from Iran indicate that opioids consumption is on the rise and is nearly three times higher in this country than in other countries; almost 1.2 million Iranians are struggling with opioid dependency.[3] Thallium is a metallic toxicant, which has high affinity for potassium binding sites and sulfhydryl

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groups.[4] Thallium is readily absorbed via inhalation, ingestion, and skin contact.[5,6]

Thallotoxicosis usually results from industrial exposure, rodenticides, and so on. In addition, some investigators indicated that the contaminating effect of thallium may be due to heroin and cocaine.[7] Several reports have confirmed that illicit opioids are highly toxic for humans.[8,9] Thallium ingestion at dosage of 8 mg/kg/body weight is toxic, and dosage of 10–15 mg/kg may result in death after few days. Several research have indicated thallium has toxic effects on various organs and tissues; such as kidney failure, harmful effects on nervous system, and heart disease.[9,10] The cellular and molecular mechanisms of thallium action are unclear yet, but some studies suggested two main mechanisms for the action of thallium. First, thallium binds to sulfhydryl groups on proteins which can result in disruption of various organ functions in heart, kidneys, and digestive and nervous systems. The second, it can replace potassium ion in the body and, via intracellular accumulation, disrupt vital protein functions, because thallium ion is a potassium ion cogener.[9–11] Thallotoxicosis, which is dose and time dependent, is associated with various signs and symptoms such as polyneuropathy, gastrointestinal problems such as diarrhea and vomiting, and respiratory problems.[12] Observed normality cutoff point for thallium concentrations is less than 5 μg/L in a 24-h urine sample.[13] Data on carcinogenic risks of thallium are extremely scanty, but what is available does not show that thallium could be carcinogenic.[14,15] Previous clinical and para-clinical studies have demonstrated thallium exposure in overdosed opioid and heroin users with a variety of gastrointestinal, neurologic, and dermatologic signs and symptoms consistent with thallotoxicosis.[16–18]

To the best of our knowledge, no study has evaluated biological samples from illicit opioid users. Better understanding of the contribution of thallium concentrations to the signs and symptoms consistent with thallotoxicosis in illicit opioid users could lead to better identification and treatment of those at risk. Therefore, we designed the present study to investigate thallium in samples from illicit opioid users and its association with severity of clinical signs and symptoms consistent with thallotoxicosis.

Methods

This case–control research was done from October 2018 to February 2019. The study group included 50 illicit opioid users (e.g. users of opium, opium residue, heroin, and mix-users) referred to Amirie Clinic in Kashan who had used illicit opioids for more than 1 year, with an age range of 18–90. The control group was composed of 50 individuals without any history of drug abuse who were relatives and close friends of the study group participants and were homogenous in terms of demographic variables (socioeconomic, sex, and age). Subjects with history of diphenoxylate, tramadol, and codeine use were excluded. Also, cases with thallium exposure in their occupational history such as solderers, battery makers, and painters were excluded to control for environmental thallium exposure. We used immunoassay tests to check for morphine in urine to confirm opioid abuse.

This study was carried out in accordance with the Declaration of Helsinki. Before admission, the study was explained to all participants and informed consent was obtained. The research was approved by the ethics committee at Kashan University of Medical Sciences (KAUMS.REC.96163).

Samples obtained from the study participants included 3 mL whole blood collected in a complete blood count tube containing anticoagulant dipotassium ethylenediaminetetraacetic acid, 10 mL urine in a plastic container from a 24-h urine sample collected by the participant, and about 200 mg hair removed from the back of the participant's head by thinning scissors and stored in a dry and cool environment. Samples (urine, blood, and hair) were collected from both study groups and were stored at −20° C until analysis. A Perkin-Elmer Model 3030 atomic absorption spectrometer equipped with transverse Zeeman background corrector, a Massmann type longitudinally heated HGA-600 graphite furnace and an AS-60 autosampler was used for the atomic absorption measurements. Perkin-Elmer pyrolytically coated grooved graphite tubes (PN B0109322) were used. Study samples had unique codes. Researchers remained blind to study participant's identity until the statistical analysis was completed. No other personnel in the laboratory had any role in this study nor were aware of the sample details. Moreover, the participants, investigators, and the assessors were unaware of the group details.

The determination of thallium in blood and urine was carried out using nitric acid and Triton X-100. We added sulfuric acid 1% (0.5 mL), nitric acid (0.5 mL), and Triton X-100 (10 mL) to blank, standard, blood, and urine samples. The mixture was vortexed and centrifuged for about 2 min. Then, 200 μL

of the modifier solution was added, and centrifuged for another 2 min, and 25 μL from the upper layer was injected into the graphite tube. To determine thallium in hair, a 200 mg sample was digested with 2 mL of nitric acid, sulfuric acid, and perchloric acid (50%, 30%, and 20%, respectively) in a boiling water bath for 1 h to give a clear yellow solution. Then, this solution was filtered with filter paper (Whatman, 150 mm) and was subsequently diluted to 0.01 L with deionized water. Then, 25 μL of diluted sample was directly injected into the graphite tube.[19–22]

Blank, standard, and control samples were prepared in a similar way. Thermal program for thallium determination (ET AAS) was the following: 130°C for drying, 300°C for organic compounds ashing, 600°C for inorganic compounds decomposition, and 1700°C for atomization. Quality control of thallium measurement was conducted at the Toxicology Laboratory of Imam Reza Hospital, Mashhad, Iran. Detection threshold of 0.2 μg/L, precision threshold of 3.65%, and accuracy threshold of 95–105% were determined through measuring and repeating biologic and thallium standard control samples (SERONORM urine trace element level 2, lot 1011645). Inter- and intra-assay of thallium were lower than 5%.

Statistical analysis of data was performed using SPSS 17 software. Quantitative data and the median (interquartile rang (IQR)) concentrations of thallium (urine, blood, and hair) in samples were compared between cases and controls using Mann–Whitney *U* test and independent samples *t*-test. Qualitative data were analyzed using Fisher's exact test and the relationship between variables was analyzed using Spearman correlation. The *p* value less than 0.05 was considered significant throughout the study to determine significance levels between groups.

Table 1. General characteristics of the study participants.[a]

Variable	Studied group ($n = 50$)	Control group ($n = 50$)	*p*-Value
Age (year)	40.9 ± 11.6	39.1 ± 8.6	0.36[b]
Age of first illicit opioids use (year)	22.4 ± 10.5	–	–
Gender; *n* (%)			
Male	46 (92)	43 (86)	0.52[c]
Female	4 (8)	7 (14)	
Marital status; *n* (%)			
Single	29 (58)	21 (42)	0.02[c]
Married	8 (16)	20 (40)	
Widow/divorced	13 (26)	9 (18)	
Job; *n* (%)			
Unemployed	30 (60)	18 (36)	0.03[c]
Employed	1 (2)	4 (8)	
Others	19 (38)	28 (56)	
Route of illicit opioid users (%)			
Smoking	25 (50)	—	—
Oral	7 (14)	—	
Smoking or oral	5 (10)	—	
Mix	13 (26)	—	
Type of illicit opioid users; *n* (%)			
Opium or opium residues	26 (52)	—	—
Heroin	8 (16)	—	
Mixed user	16 (32)	—	
Cigarette smoking; *n* (%)			
Yes	47 (94)	2 (4)	<0.0001[c]
No	3 (6)	48 (96)	

[a]Data are mean ± SD and percentage.
[b]Obtained from independent samples *t*-test.
[c]Obtained from Fisher's exact test.

Results

Demographic characteristics

Overall, 100 subjects, 50 in the study group and 50 in the control group, were recruited. Of the 100 individuals, 89 (89%) were male and 11 (11%) were female. Also, in the studied group, 47 patients (94%) and two subjects (4%) in the control group had a cigarette consumption. Participants age ranged from 21 years to 86 years with a mean age and SD of 40.9 ± 11.6 years. The mean age of first illicit drug use was 22.4. The mean age (SD) of the control group was 39.1 ± 8.6 years (range 23–63 years). The mean (SD) and range of duration of illicit opioid use were 11.5 ± 7.3 and 1–27, respectively. Daily average frequency of illicit opioid use for the study group was 2.5 ± 0.9 (range: 1–6 per day; Table 1).

Thallium concentrations

Median (IQR) concentrations of urine thallium was 54.8 ± 79.9 and 4.8 ± 5.2 μg/L for the study and the control groups, respectively ($p < 0.001$). Also, median blood thallium concentrations in the study group were 14.5 ± 11.1 μg/L, higher than the comparable concentrations in the control group with a median of 2.5 ± 2.4 μg/L ($p < 0.001$). Median hair thallium concentrations were 5.4 ± 3.7 and 1.4 ± 1.1 μg/g for the study group and the control group, respectively. There was a significant difference in hair thallium concentrations between study and control groups ($p < 0.001$; Table 2).

Table 2. Thallium concentrations in urine, blood, and hair (μg/L or μg/g).[a]

Variable in two groups	Concentration of thallium (μg/L or μg/g)		*p*-Value[b]
	Study ($n = 50$); min − max	Control ($n = 50$); min − max	
Urine thallium	54.8 (79.9); 15.1 − 267	4.8 (5.2); 1.7 − 19.6	<0.001
Blood thallium	14.5 (11.1); 4.4 − 43.4	2.5 (2.4); 0.6 − 9.1	<0.001
Hair thallium (μg/g)	5.4 (3.7); 1.8 − 14.9	1.4 (1.1); 0.4 − 5.0	<0.001

IQR: interquartile range.
[a]Data are median (IQR).
[b]Obtained from Mann–Whitney *U* test.

There was a significant correlation between the duration of illicit opioid use and urine thallium concentrations ($r = 0.394$, $p = 0.005$), as well as hair thallium concentrations ($r = 0.293$, $p = 0.039$), but not with blood thallium concentrations ($r = 0.246$, $p = 0.085$; Figure 1).

Urine, blood, and hair thallium concentrations were not statistically different according to the route of opioid administration, and the type of the drug abuse. Moreover, urine, blood, and hair thallium concentrations were not statistically different based on frequency of daily use.

Clinical signs and symptoms

The incidence of positive clinical signs and symptoms consistent with thallotoxicosis in the study group was higher than the comparable incidence in the control group. In the study group, mean concentrations of urine and blood thallium were significantly higher in those presenting with weakness ($p = 0.01$), depression ($p = 0.03$), and headache ($p = 0.03$), compared to those who did not manifest these signs and symptoms. Clinical signs and symptoms consistent with thallotoxicosis and thallium concentrations in the studied groups are shown in Tables 3 and 4.

Discussion

In this study, we found that the urine thallium concentrations were significantly higher than the mean thallium concentrations in blood and hair in the two groups. Furthermore, concentrations of thallium in urine, blood, and hair were significantly higher than those of the control group. To the best of our knowledge, this is the first time when thallium concentrations in urine, blood, and hair, as well as clinical signs

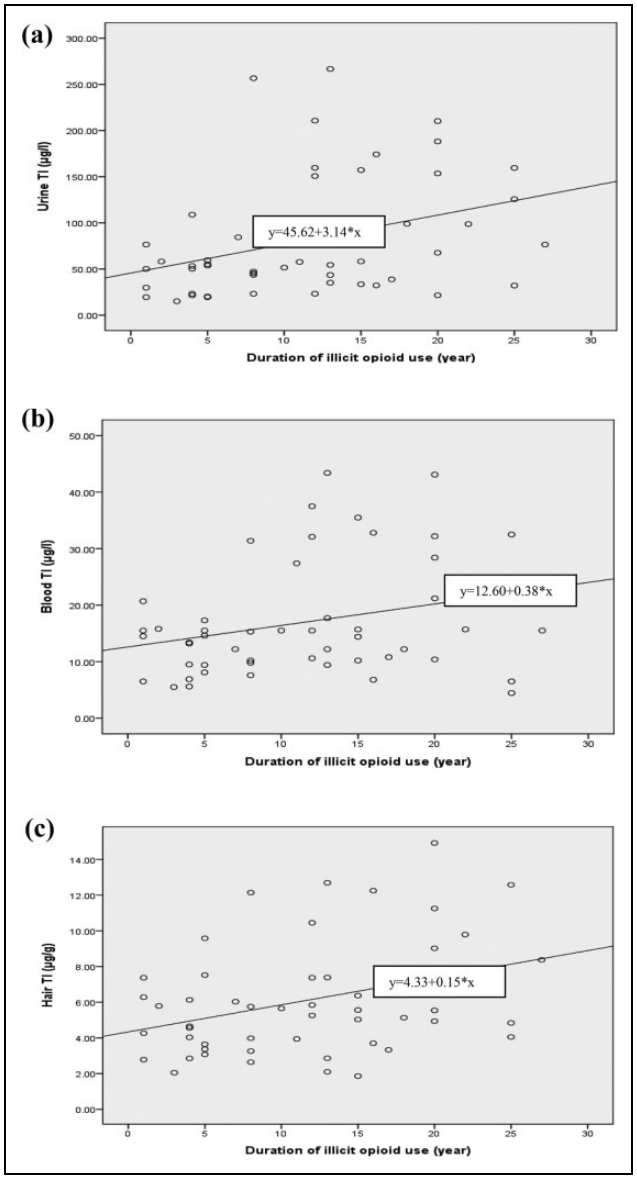

Figure 1. (a) to (c) Correlation between the duration of illicit opioid use with urine, blood, and hair thallium concentrations.

Table 3. Frequency of clinical signs and symptoms and urine, blood, and hair thallium concentrations in the studied groups (μg/L or μg/g).[a]

Clinical symptoms		Positive (%)	Urine thallium	*p*-Value[b]	Blood thallium	*p*-Value[b]	Hair thallium (μg/g)	*p*-Value[b]
Neurological signs and symptoms	Weakness	31 (62%)	97.5 ± 72.7	0.01[c]	17.5 ± 11.5	0.58	6.2 ± 3.6	0.54
	Fatigue	25 (50%)	81.4 ± 61.8	0.99	16.2 ± 10	0.62	5.5 ± 3	0.27
	Paresthesia	19 (38%)	86.9 ± 57	0.65	17.1 ± 10.5	0.93	6.2 ± 3.3	0.82
	Ataxia	21 (42%)	83.6 ± 54.3	0.85	16 ± 9.2	0.60	5.7 ± 2.8	0.58
	Vertigo	26 (52%)	71.2 ± 52.9	0.25	15 ± 8.8	0.17	5.3 ± 2.7	0.07
	Blurred vision	16 (32%)	85.3 ± 65.6	0.78	16 ± 10.1	0.65	5.5 ± 2.6	0.43
	Memory deficits	27 (54%)	84.8 ± 71	0.70	17.6 ± 10.5	0.60	5.8 ± 2.7	0.65
	Tremor	20 (40%)	86.7 ± 63.7	0.65	16.7 ± 9.6	0.91	5.6 ± 3	0.43
	Aggressiveness	33 (66%)	89.5 ± 74.1	0.15	18.4 ± 11.5	0.08	6.2 ± 3.3	0.65
	Jerking movements	15 (30%)	85 ± 67.2	0.80	15.7 ± 9.7	0.57	5.3 ± 2.6	0.27
	Insomnia	33 (66%)	87.7 ± 70.2	0.36	64.4 ± 10	0.61	6.2 ± 3.1	0.70
	Seizures	9 (18%)	77.3 ± 48.5	0.83	15.6 ± 9	0.66	5.5 ± 2.6	0.61
	Depression	21 (42%)	106.9 ± 82.7	0.03[c]	19.2 ± 12.7	0.22	6.5 ± 3.9	0.40
	Tinnitus	15 (30%)	80.9 ± 61.6	0.96	17.2 ± 11.9	0.91	5.5 ± 3.4	0.49
	Delirium-psychosis-coma	2 (4%)	49.4 ± 8.1	0.48	14.9 ± 0.4	0.78	3 ± 0.5	0.16
	Headache	18 (36%)	64.4 ± 46.3	0.12	13.1 ± 7.6	0.03[c]	5.1 ± 2.5	0.11
	Emotional liability	10 (20%)	91.3 ± 62.2	0.60	21.1 ± 13	0.26	6.9 ± 3.8	0.34
	Choreoathetosis	4 (8%)	44.8 ± 20.5	0.24	14.5 ± 9.9	0.62	3.3 ± 1.2	0.07
Dermatological signs and symptoms	Scalp hair loss	27 (54%)	94 ± 72.3	0.13	17.1 ± 11.5	0.90	6.4 ± 3.4	0.37
	Body hair loss	3 (6%)	122.4 ± 79.2	0.27	23.9 ± 10.4	0.23	6.5 ± 3.4	0.81
	Sweating	32 (64%)	88.4 ± 70.4	0.29	17.6 ± 11.1	0.50	6.3 ± 3.4	0.39
	Rashes	7 (14%)	60.5 ± 51.3	0.36	14.3 ± 10.4	0.47	4.9 ± 2	0.30
	Dry skin	12 (24%)	70.5 ± 49.3	0.50	18.1 ± 10.4	0.64	6.1 ± 2.7	0.97
	Mees' lines	7 (14%)	95.3 ± 63.1	0.55	20.1 ± 11.8	0.38	6.2 ± 1.8	0.85
	Acne	8 (16%)	66.3 ± 50.7	0.47	13.5 ± 10.1	0.31	4.7 ± 2	0.21
	Palmar erythema	0 (0%)	—		—	—	—	—
Gastrointestinal signs and symptoms	Constipation	27 (54%)	85.7 ± 66.6	0.62	17.9 ± 9.8	0.46	6 ± 3.1	0.96
	Abdominal pain	19 (38%)	77.4 ± 57.1	0.73	16.8 ± 9.6	0.95	5.8 ± 2.3	0.71
	Nausea	9 (18%)	90.6 ± 69.9	0.65	18.6 ± 13.1	0.59	6.9 ± 3.7	0.37
	Vomiting	8 (16%)	79.6 ± 54.3	0.92	16.1 ± 9.6	0.80	6.3 ± 2.3	0.78
	Diarrhea	9 (18%)	74.7 ± 52.8	0.73	14.9 ± 9.7	0.52	5.8 ± 2.2	0.82

[a]Data are mean ± SD and percentage.
[b]Obtained from independent samples *t*-test.
[c]Significance level $p < 0.05$.

and symptoms consistent with thallotoxicosis in illicit opioid users, have been evaluated.

In the control group, small amounts of thallium was found in their urine, blood, and hair, which might be due to enhanced status of thallium in natural environment, fruits, crops, and livestock entering human body via the food cycle.[23] In fact, Karbowska[23] demonstrated that thallium concentrations is higher in heavy waters used by humans due to its more solubility compared to other metals. Previous evidence have reported that illicit drugs may have lead, thallium, and steroids impurities.[16,17,24] Thallium concentrations in illicit drugs are low, but when taken in large amounts, opioids adulterated with thallium can produce clinical (e.g. neurological, gastrointestinal, and dermal) problems. Despite of extensive research, very few evidence-based study indicate exotic and unusual cases of chronic thallotoxicosis due to use of adulterated opioids.[16–18] Ghaderi et al.[16] showed that urinary thallium concentrations in opioid poisoned patients were 21 μg/L compared to 1 μg/L in healthy people. In another study, probable thallotoxicosis was reported in three cases in three overdosed heroin users. The semiquantitative thallium concentrations in these three cases was 200–300 μg/dL; 12 weeks after starting opioid substitution therapy, signs and symptoms consistent with thallotoxicosis resolved; and it was concluded the heroin was contaminated.[17] In addition, Questel et al. reported two cases of heroin users with signs and symptoms consistent with thallotoxicosis.[18] It has been demonstrated that some smugglers and salesmen may add

Table 4. Frequency of clinical signs and symptoms and urine, blood, and hair thallium concentrations in the control group (μg/L or μg/g).[a]

Clinical symptoms		Positive (%)	Urine thallium	*p*-Value[b]	Blood thallium	*p*-Value[b]	Hair thallium (μg/g)	*p*-Value[b]
Neurological signs and symptoms	Weakness	7 (14%)	7.2 ± 3.8	0.58	3.2 ± 2.7	0.97	1.6 ± 1.5	0.89
	Fatigue	4 (8%)	5.4 ± 2.2	0.58	2 ± 0.4	0.25	1.2 ± 0.1	0.32
	Paresthesia	2 (4%)	5.1 ± 2.7	0.65	2.3 ± 0.2	0.59	1.1 ± 0.4	0.37
	Ataxia	1 (2%)	7.1	0.87	2.5	0.73	1.4	0.81
	Vertigo	4 (8%)	5.4 ± 3.2	0.61	1.9 ± 1.1	0.21	1.2 ± 0.6	0.40
	Blurred vision	4 (8%)	5.6 ± 2.8	0.68	3 ± 2.1	0.88	1.9 ± 0.8	0.60
	Memory deficits	5 (10%)	5.3 ± 5	0.52	3.3 ± 3	0.87	1.8 ± 1.2	0.65
	Tremor	2 (4%)	12.1 ± 10.6	0.57	5.9 ± 3.6	0.46	3.1 ± 1	0.27
	Aggressiveness	10 (20%)	4.9 ± 2.2	0.07	2.5 ± 1.4	0.23	1.2 ± 0.6	0.16
	Jerking movements	0 (0%)	—	—	—	—	—	—
	Insomnia	11 (22%)	6.8 ± 5.6	0.74	3.1 ± 2.8	0.96	1.7 ± 1.2	0.67
	Seizures	1 (2%)	3.2	0.41	2.2	0.62	0.8	0.37
	Depression	6 (12%)	5.8 ± 4.1	0.71	3.2 ± 2.2	0.90	1.7 ± 0.9	0.89
	Tinnitus	2 (4%)	6.9 ± 2.4	0.86	4.1 ± 2.1	0.49	2.3 ± 0.6	0.31
	Delirium-psychosis-coma	0 (0%)	—		—	—	—	—
	Headache	12 (24%)	5.6 ± 4.7	0.42	2.7 ± 2	0.37	1.5 ± 0.9	0.59
	Emotional liability	2 (4%)	6.9 ± 2.4	0.86	4 ± 2.4	0.56	2.4 ± 0.5	0.27
	Choreoathetosis	0 (0%)	—	—	—	—	—	—
Dermatological signs and symptoms	Scalp hair loss	19 (38%)	5.8 ± 3.9	0.41	2.6 ± 1.7	0.14	1.3 ± 0.8	0.06
	Body hair loss	0 (0%)	—	—	—	—	—	—
	Sweating	4 (8%)	7 ± 4.1	0.75	2.9 ± 1.7	0.79	1.3 ± 0.7	0.45
	Rashes	0 (0%)	—	—	—	—	—	—
	Dry skin	2 (4%)	2.7 ± 1.3	0.18	1.4 ± 0.7	0.21	5.8 ± 3.9	0.25
	Mees' lines	0 (0%)	—	—	—	—	—	—
	Palmar erythema	0 (0%)	—	—	—	—	—	—
	Acne	2 (4%)	6.5 ± 3.3	0.98	2.3 ± 1.6	0.55	0.9 ± 0.2	0.99
Gastrointestinal signs and symptoms	Constipation	7 (14%)	4.8 ± 2.2	0.26	1.9 ± 0.7	0.09	1.3 ± 0.5	0.37
	Abdominal pain	2 (4%)	6.5 ± 1.9	0.97	2.6 ± 0.4	0.67	2	0.62
	Nausea	1 (2%)	5.2	0.75	2.3	0.66	2	0.70
	Vomiting	1 (2%)	5.2	0.75	2.3	0.66	2	0.70
	Diarrhea	1 (2%)	5.2	0.75	2.3	0.66	2	0.70

[a] Data are mean ± SD and percentage.
[b] Obtained from independent samples *t*-test.

adulterated material often contaminated with high concentrations of heavy metals (e.g. thallium and lead), as well as some medications to enhance the weight and the impact of the illicit drugs. Illegal laboratories refine opium into a brown sticky paste, pressed into bricks and sun dried, which then can be smoked or ingested. During this process, impurities maybe introduced into the opium.[17,25]

On the other hand, cigarette smoking is also a source of exposure to thallium. Thallium concentrations in the body of smokers were twice higher than those of the healthy subjects.[26] Another study reported thallium concentrations were significantly higher in smokers compared to the healthy control group.[27] Considering that a large number of the study group members were smokers, probably an amount of thallium in their bodies is related to cigarette smoking.

Our study demonstrated that the most frequent clinical signs and symptoms consistent with thallotoxicosis were insomnia, aggressiveness, weakness, sweating, scalp hair loss, abdominal pain, and constipation, which are, to some extent, different from signs and symptoms reported by other studies, that is, polyneuropathy, hair loss, muscle weakness, and abdominal pain.[4,9,28] In another study, Ghaderi et al.[16] showed the most prevalent clinical signs and symptoms consistent with thallotoxicosis were tremor, ataxia, sweating, insomnia, scalp hair loss, dry skin, constipation, vomiting, and nausea in overdosed opioid patients. In addition, neuro-psychological effects of thallium exposure have been demonstrated previously which includes memory deficit, depression, and insomnia.[16,29,30] Seizure is an adverse effect of tramadol consumption. In Iran, a large number of

illicit opioid users also abuse tramadol to achieve euphoria and as a replacement for other opioids.[31,32] In this study, 18% of opioid drug users had a history of seizure which seems to be a result of combined opioid and tramadol abuse.[33–35]

The results suggested that illicit opioids are an important source of exposure to thallium in Iran. Therefore, physicians need to be aware of the clinical signs and symptoms consistent with thallotoxicosis in illicit opioid users.

Limitations

Our study had some limitations, including sample size; for more accurate results, bigger sample sizes are warranted. Also, we were not able to accurately identify the source of thallium in illicit opioid users who smoked cigarettes, because low sample size; therefore, evaluating thallium source in this group is suggested for future studies. Additionally, more studies are needed to identify the reason for the relatively common occurrence of some clinical signs and symptoms consistent with thallotoxicosis (gastrointestinal, neurological, and dermal) in illicit opioid users. Moreover, we did not accurately evaluate the symptoms are related to thallium. Further studies are needed to determine the symptoms related to thallium. Another limitation was the use of matched controls. Matching was done based on age, sex, and socioeconomic factors. Cigarette smoking was not completely matched between two groups, therefore conclusion regarding the effect of illicit opioids on thallium concentrations should be interpreted with caution. Also, in the current study, we did not assess thallium in illicit opioid. This should be considered in the interpretation of our findings.

Conclusions

Overall, it was observed that the illicit opioid users had more thallium in their blood, urine, and hair than those in the healthy subjects. Therefore, screening illicit opioid users for thallium concentrations will be helpful, especially for those with non-specific signs and symptoms consistent with thallotoxicosis.

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Availability of data and material

The primary data for this study is available from the authors on direct request.

Author contributions

NM, AG, and HRB contributed in design, conception, and statistical analysis. NM, AG, and HRB contributed in data collection and manuscript drafting.

Declaration of conflicting interests

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Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

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