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Research Article

Heroin-Induced Endocrinopathies in Female Addicts

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Abstract
Background: Substance use disorder is a global issue that affects not only the physical and mental health of individuals but also the employment and health of entire countries. Substance addiction is one of the persistent global issues that affects individuals of various ages, socioeconomic backgrounds, areas, levels of education, and countries. Males were believed to be more likely than females to suffer from heroin use disorder. Nonetheless, it was shown that the frequency of heroin use is rising more quickly among women. The goal of this study was assessing several endocrine disorders in female heroin addicts and the socio-demographic characteristics.
Methods: The study was a comparative cross-sectional study done in Al-Abbassya Mental Hospital affiliated to General Secretariat of the Mental Health Hospitals, Psychiatry and Neurology Center and Neuropsychiatry Department, Tanta University. The research was conducted from June 2022 through March 2024 over a period of 22 months.
Results: All the study's selected addicts (50) were female smokers between the ages of 20 and 30 (mean = 25.46 ± 2.65). Regarding levels of education, there was not a significant difference between the study groups (P=0.071). In terms of marital status, there was a notable difference between the addicts and the control group (P=0.015). Female addicts had a higher divorce rate. Seventy percent of heroin addicts were from urban areas which means that heroin addiction is more common in urbans in comparison to rurales with no significant difference between the study groups. The control group and the addicts' group differed significantly in terms of smoking index (P=0.001), as the addicts' group had a higher mean than the control group. Total testosterone, estradiol, luteinizing hormone, and follicular stimulating hormone levels were significantly lower in heroin addicts than the control groups (P <0.001).
Prolactin levels were significantly higher in heroin users than in the control groups (P <0.001), indicating a substantial difference between the two groups.
Conclusions: Heroin use disorder in females caused significant low total testosterone, estradiol, luteinizing hormone and follicular stimulating hormone levels. Heroin use disorder in females led to a significant elevated level of prolactin.

Keywords: Heroin use disorder in females, socio-demographic characteristics, total testosterone, estradiol, luteinizing hormone, follicular stimulating hormone, prolactin level.

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Introduction:

Addiction is a brain illness characterized by recurrent episodes of chronicity and compulsive substance use despite negative outcomes **(Andreas et al., 2019)**.

Men have traditionally been linked to drug abuse. Studies in a variety of fields, such as behavioral pharmacology, neurology, and epidemiology, have analyzed the variables and/or interventions that impact drug usage from a male-centric perspective. The underlying causes of drug abuse in women have been overlooked. As a result, it is unclear how widespread drug usage occurs among women and what consequences it has **(Anker et al., 2011).**

Current studies on substance abuse reveal notable variations between genders in the epidemiology of substance use **(Erskine et all., 2015).** Significant differences were also found between the two genders regarding social factors, biological reactions, stages of dependence, health outcomes, co-occurring mental illnesses, and obstacles to start, stay in, and finish treatment **(Tuchman 2010).**

Women showed a quicker transition from use to dependence **(Becker and Hu, 2008),** They present with worse clinical conditions at the time of admission, more frequent comorbidity for depression and anxiety, increased suicide risk, and worse physical health compared to men presenting opioid use disorder **(Zamboni et al., 2019).** In addition, women may be more susceptible to craving and relapse **(Kennedy et al., 2013).**

Opioids inhibit the production of multiple hypothalamic, pituitary, ovarian and adrenal hormones, causing opioid-induced hypogonadotropic hypogonadism that can determine amenorrhea or hypomenorrhea, sexual dysfunctions (SDs), fatigue and depression in female addicts **(Rhodin et al., 2010).**

Hypogonadism is the most well recognized hormonal consequence of opioid use, but the inhibitory effects of opioid drugs on the hypothalamo–pituitary–adrenal axis and their negative effects on bone health also require attention **(Wehbeh et al., 2020).**

Hyperprolactinaemia might be detected in opioid users. Assessment of gonadal and adrenal function (particularly if high index of clinical suspicion of hypogonadism or hypoadrenalism) is advised in people that use opioids. **(Fountas et al., 2020).**

Methods:

The aim of this study was to assess some endocrinal disturbances among female heroin addicts. The study was a comparative cross-sectional study done in Al-Abbassya Mental Hospital affiliated to General Secretariat of the Mental Health Hospitals, Psychiatry and Neurology Center and Neuropsychiatry Department, Tanta University. The research was conducted from June 2022 through March 2024 over a period of 22 months. Fifty female patients who met the DSM-5 criteria for heroin use disorders. A control group of fifty healthy female smokers was selected to match addicts group.

Inclusion criteria:

All participants included in this study were female smokers abusing heroin by any means. Females aged from 20 to 30 years old to avoid normal hormonal changes that occur with age. Heroin addicts who have abused the drug for at least a year, taking 100 mg or more per day. Females with a body mass index of 25–30, since hormonal cycles may be impacted by being overweight or underweight. All participants were able to read and write to fill out the evaluation forms.

Exclusion criteria:

Women who were younger than 20 and older than 30. Women who were pregnant or nursing, either at time of assessment or within the last 12 months. Women whose body mass index is between 25 and 30. Women who had a problematic menstruation cycle before using heroin. Current substance use disorder other than heroin "except smoking". Patients who have used medications that may have an impact on the hormones being studied, such as progesterone, estrogen, steroids, or antipsychotics, for the last two years. Patients with conditions such as hepatic, renal, evident acute or chronic infections, systemic inflammatory disease, malignancy, autoimmune disorders, sexual organ surgery, or pituitary gland problems that may impact the hormones being studied or result in hypogonadism. Patients suffering from diseases that could affect the menstrual cycle e.g., thyroid dysfunction, poly-cystic ovaries, etc. Patients with either impaired consciousness (e.g., during severe intoxication/withdrawal, secondary to sedation or post-ictal state, as determined by history and clinical assessment) or those with active manic and/or psychotic symptoms that may hinder study participation.

All participants in this study were subjected to the following:

- History taking: Personal, present, past history and drug history (dose, duration, route of intake, causes for abuse).
- Clinical examination: systemic and neurological examination to implement exclusion criteria.
- Mental state examination: Mini International Neuropsychiatric Interview (MINI) Arabic version 7.0.2 **(Churbaji et al., 2019).**
- Laboratory Investigation:

1. Hormonal assay of the serum levels of: Total Testosterone, Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Estradiol, and Prolactin.
2. Appropriate other investigations if needed:

- Renal and or liver functions to exclude renal or hepatic diseases.
- Drug screening of urine for exclusion of polysubstance abuse.

Statistical analysis

Data were analyzed using the IBM® SPSS statistical software, version 27, created by IBM, Chicago, Illinois,

USA. We used the one-sample Kolmogorov—Smirnov test to check the normality of data and the data were parametric. Numerical data was presented as mean and standard deviation (SD) and categorical data was presented as number and percentage.

Chi-squared test was used for comparing the qualitative data. Standard student "t test", is a test of significance of the difference between two means.

One Way of Anova test (ONOVA) test was used to compare the means in different groups. Significance between groups was done using Post Hoc Test (LSD test). The level of significance was adopted at $p<0.05$.

Results

In the study, all the selected addicts were female smokers *aged* 20 to 30 years old (mean = 25.46 ± 2.65) **Table (1).** Most heroin users (76%) did not have a job, and this difference was significant between the addicts and the control group (P=0.035*) **Table (2)**. Regarding levels of education, there was not a significant difference between the study groups (P=0.071) **Table (3).**

Seventy percent of heroin addicts were from urban areas which means that heroin addiction is more common in *urbans* in comparison to rurales with no significant difference between the study groups **Table (4).** Regarding marital status, there was a significant difference between the control group and the addicts (P=0.015). Female addicts had a higher divorce rate **Table (5).**

The addicts' group had a significantly higher mean of smoking index compared to control group(P=0.001) **Table (6).** Total testosterone, estradiol, luteinizing hormone, and follicular stimulating hormone levels were significantly lower in heroin addicts than in the control groups (P <0.001). Also, there were significant differences between the two groups **Table (8-11).**

There was significant difference of prolactin level between the addicts and the control groups, as heroin addicts had a significant high level of prolactin (P <0.001) **Table (7).**

Discussion

The range of age in the participants was from 20 to 30 years to avoid hormonal swings that could unpredictably occur. According to the current study, the control group's mean age was 24.98 ± 3.09, whereas the addicts' mean age was 25.46 ± 2.65.

The difference between the addicts and the control groups in terms of employment was statistically significant (P = 0.035). Most of heroin addicts were *unemployed* (76.0%). These results agreed with Grella and colleagues (2012) and Zhou and colleagues (2017) who suggested that women with heroin use were likely to be unemployed than general population. Additionally, it was shown by Nolte-Troha and colleagues (2023) that using illegal drugs was linked to greater unemployment rates. Furthermore, there was a correlation between increased rates of illicit drug use and unemployment.

Diehl and colleagues (2016) emphasized that women with substance use disorder were characterized predominantly by being unemployed, unmarried, and with low income. Unemployment and opioid usage were significantly positively correlated, with higher unemployment rates being linked to higher rates of opioid use in both sexes (Van Draanen et al., 2020). On the contrary, Amr and colleagues (2014) found that there was no statistically significant difference regarding employment, in both sexes with various substance use.

While Loffredo and colleagues (2015) suggested that work stress might be a risk factor for substance abuse in some circumstances. They claimed that young women commonly use drugs as a kind of self-medication to deal with psychological stress and frustration. This aids in their ability to overcome past painful memories and get over any physical discomfort they might be feeling at work.

There was no statistically significant difference between the addicts and the control groups regarding the *educational* level (P =0.71). This means that addicts with different educational levels, apart from illiterates as were deducted from the study, were similarly affected by substance abuse. This may be related to small number of participants in comparison to other studies. This comes in agreement with Caton and colleagues (2005) who reported no significant difference in both sexes between the addicts and control groups regarding level of education.

In contrast, Puigdollers and colleagues (2004) reported low educational level were high in heroin addicts of both sexes. Also, the results of the Egyptian national addiction survey showed substance abuse including opiates had higher lifetime prevalence among less educated persons (Hamdi et al, 2016). In addition, EL-Sherbiny 2015 concluded that drug abuse among university graduates (4.1%) was significantly lower compared with that among illiterate (54.5%) and literate (27.5%) individuals.

There is a clear inverse relationship between degree of education and the prevalence of substance use in many studies. El-Sawy and colleagues (2010) found that most of the patients with various substance abuse had low educational level. Moreover, a significant negative association between measures of education and opioid use was demonstrated where, higher levels of educational attainment were associated with lower rates of opioid-use. This may be because higher educational levels provide the knowledge to make healthier personal choices and ways to avoid an individual from getting into risky situations or behaviors (Van Draanen et al, 2020).

Regarding *residence*, there was no significant difference between the heroin addicts and the control group (P =0.36), although 70% of heroin addicts were from urban areas. This means that heroin addiction is more common in urban areas in comparison to rural areas. However, as our study had a few limitations that might have affected the genuine prevalence of heroin in various residency areas, it shouldn't be taken for granted. The results of the Egyptian national addiction survey which the general secretariat of mental health performed since 2016 that showed substance abuse including opiates had higher lifetime prevalence among those living in urban areas (Hamdi et al, 2016).

El-Ghonemy and colleagues (2021) demonstrated that being from Cairo or high family income were positively associated with substance use among female university students. Hamdi and colleagues (2016) explained the finding by the openness of the female social life in Cairo, which implies more stresses on the females living there, and makes it easy for them to reach the drug dealer areas. Also, a significant predominance of urban residency in patients with substance abuse (El-Sawy et al, 2010).

People of rural origins are the least at using substance(s). This is probably related to the stronger family bonds and social relations in the countryside, and the difficulty to isolate and hide people suffering from substance use and abuse, for fear of stigma (Hamdi et al, 2016).

This may be due to drug substance is easily accessible and available in the urban areas and addicts are more vulnerable to stressful lifestyle and have higher income more than rural areas this comes in agreement with EL-Sherbiny 2015 who found that drug abuse was significantly higher among individuals of urban residence (24.1%) than among those of rural residence (6.4%). While Mohamed and colleagues (2015) found no statistically significant association between the residence and the use of substance. This may be due to availability of substance of abuse in rural and urban areas and due to urbanization of rural areas.

There was a significant difference between the addicts and the control groups as regards to *marital status* (P =0.015). Divorce rate was higher in female addicts. Addicts were less likely to be committed to a stable relationship than the controls. This comes in agreement with Amr and colleagues (2014) who found that being younger, unmarried, and having unsatisfactory income were significant risk factors of various substance abuse. El-Sawy and colleagues (2010) also found that most of the studied addicts were not married. Moreover, the current study agreed with the results of the Egyptian National Addiction Survey that showed that substance abuse, including opiates, had higher lifetime prevalence among those with failed marriage (Emad et al, 2016). Diehl and colleagues (2016) emphasized that women with substance use disorder were characterized predominantly by being unmarried, unemployed, and with low income.

All participants were smokers. There was a significant difference regarding smoking index between the control and the addicts' group (p =0.001). Smoking index was significantly higher among heroin addicts compared to the control group. Our study was in concordance with Bassiony and colleagues (2024) who suggested that patients with heroin use were more likely to have a higher smoking rate. Also, Rabie and colleagues (2020) highlighted the prevalence of nicotine use among the young females, which was the most used substance during lifetime (4.18%). Even though females undoubtedly smoke less in our society because of cultural, social, and familial restrictions (El-Gilany et al., 2008).

There was significant difference between the addicts and the control groups regarding total testosterone level, as heroin addicts had significant low total testosterone (P <0.001). This agreed with Katz and Mazer (2009) who suggested that long-term opioid therapy for either addiction or chronic pain often induces hypogonadism due to central suppression of hypothalamic secretion of gonadotropin-releasing hormone in both sexes.

Aloisi and colleagues (2010) explained the reduction of testosterone secretion is mainly attributed to opioid-induced suppression of gonadotropin releasing hormone (GnRH) release from hypothalamus. Additionally, opioids enhance the breakdown of testosterone by causing an evident change in the expression of 5-α-reductase type 1 mRNA (responsible for the conversion of testosterone to dihydrotestosterone in peripheral body tissues). This might act as a peripheral mechanism of androgen suppression. Moreover, Bhasin and colleagues (2007) found that opioids have an inhibitory effect on serum total and free testosterone concentrations in women.

Furthermore, suppression of adrenal androgen release plays a role in opioid-induced hypogonadism, which has been demonstrated by Daniell and colleagues (2006) in a case-control study with participation of 152 addicts of both genders. Cepeda and colleagues (2015) also showed that having low levels of total testosterone is prevalent in heroin addicts in both women and men. Findings were like Miller and colleagues (2001) who revealed that the endocrine systems of women can also be affected by opioids. "Women with hypopituitarism and secondary hypogonadism have been found to have reduced levels of total testosterone, free testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) levels as compared with healthy controls." Moreover, George and colleagues (2005) demonstrated the effects of heroin misuse on the human endocrine system by reductions in testosterone levels; and abnormalities in follicular stimulating hormone/luteinizing hormone (FSH/LH) levels.

On the other hand, Bawor and colleagues (2014) demonstrated that there was no significant effect of opioids on testosterone level in opioid-using women (n = 121) compared to controls (n = 512), but it should be highlighted that methadone was used in this study. Thus, not all types of opioids may alter testosterone level. Additionally, Daniell 2008 reported that methadone use to control nonmalignant pain in women did not affect testosterone level in comparison to non–opioid-consuming control subjects.

We reported a significant difference of prolactin level between the addicts and the control groups, as heroin addicts had a significantly high level of prolactin (P <0.001). Moshtaghi-Kashanian and colleagues (2005) revealed a significant higher prolactin concentration compared with healthy people and cases of hyperprolactinaemia have been detected in people addicted to heroin and in people who smoke opium. Opioid-induced hyperprolactinaemia can lead to painful gynecomastia, galactorrhea, and hypogonadism (Rhodin et al., 2010).

Katz and Mazer 2009 described amenorrhea and galactorrhea in female heroin addicts. This result is consistent with de vries and colleagues (2019) who reported high prolactin secretion by the effect of opioids. Moreover, Rhodin and colleagues (2010); Wong and

colleagues (2011) showed an increase in serum prolactin levels among patients on opioid analgesics. Antony and colleagues (2020) also highlighted that opioids have been shown to increase pituitary release of prolactin in preclinical studies, which, in turn, decreases testosterone secretion. Opioids can have a stimulatory effect on prolactin secretion mediated by μ-, κ- and δ-opioid receptors in the hypothalamus (Fountas et al., 2018).

On the other hand, Aloisi and colleagues (2009) demonstrated that prolactin is increased in initial opioid therapy, and this is followed by regression to normal values upon chronic opioid therapy. Merdin and colleagues (2016) reported that only 40% of addicts had hyperprolactinemia.

In the current study, there were significant differences of both luteinizing hormone and follicular stimulating hormone levels between the addicts and the control groups, as heroin addicts had significant low luteinizing hormone and follicular stimulating hormone ($P < 0.001$). Opioids have been shown to decrease the release of the normal pulsatile nature of gonadotropin-releasing hormone (GnRH) secretion and reduction of the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland, and of testosterone or estradiol from the gonads (Vuong et al., 2009; Fraser et al., 2009; Fountas et al., 2018).

Consistent with Katz and Mazer, 2009 who suggested that long-term opioid therapy for either addiction or chronic pain often induces hypogonadism lowering luteinizing hormone and follicle-stimulating hormone owing to central suppression of hypothalamic secretion of gonadotropin-releasing hormone in both sexes. Daniell and colleagues (2008) also reported that luteinizing hormone and follicle-stimulating hormone values were lower in patients using opioids to control nonmalignant pain compared to control subjects using non–opioid analgesics.

Elliott and colleagues (2012) documented hypogonadism with decreased luteinizing hormone and follicle-stimulating hormone levels in both males and females as early as one week after starting opioid therapy, with luteinizing hormone levels more affected in males. In addition, George and colleagues (2005) demonstrated the effects of heroin misuse on the human endocrine system by reductions in follicular stimulating hormone and luteinizing hormone levels.

There was significant difference of estradiol level between the addicts and the control groups, as heroin addicts had significantly low estradiol level ($P < 0.001$). Sex hormones in males and females are under the control of the hypothalamo-pituitary-gonadal (HPG) axis. Opioid hypogonadism is attributed to a derangement of the pulsatile release of hypothalamic GnRH with consequent estrogen, progesterone, deficiency of luteinizing hormone (LH) follicle-stimulating hormone (FSH), and androgens (Antony et al., 2020; Vuong et al., 2009; Fraser et al., 2009; Fountas et al., 2018).

Katz and Mazer 2009 reported decreased levels of estradiol and progesterone in women with opiate use. Merza and colleagues (2010) suggested that long term use of opioids in patients with heroin addicts or with chronic pain may lead to abnormalities in the endocrine system including sex hormones as low estradiol level. On the contrary, Wong and colleagues (2011) found that serum estradiol was not affected in women opiate addicts.

Conclusions:

Employment and marital status were significantly affected in female heroin addicts. Heroin addicts were less likely to be committed to a stable relationship than the controls. All heroin addicts with different educational levels were affected with no significant differences compared to control group.

The levels of luteinizing hormone, follicular stimulating hormone, total testosterone, and estradiol are significantly low in females with heroin use disorder. Females with heroin use disorder had significantly higher prolactin levels.

List of abbreviations

DHEAS Dehydroepiandrosterone Sulfate
DSM-5 Diagnostic and Statistical Manual for Mental Disorders, Fifth Edition
FSH Follicle-stimulating hormone
GnRH Gonadotropin-Releasing Hormone
GSMHAT General Secretariat of Mental Health, And Addiction Treatment
HPA Hypothalamic Pituitary Adrenal
HPG Hypothalamic Pituitary Gonadal
LH Luteinizing Hormone
MINI Mini International Neuropsychiatric Interview
MOH Ministry of Health
PRL Prolactin
SUD Substance Use Disorder

Declaration

Ethics approval and consent to participate.

This research was carried out from June 2022 through March 2024 over a period of 22 months, after receiving approval from the Ethical Committee at Tanta University Hospitals in Tanta, Egypt.

Consent for publication

An informed written consent was obtained from all participants.

Availability of data and material

Data and material are available on a reasonable request from the author.

Competing interests

The authors have no financial or proprietary interests in any material discussed in this article.

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Tables

Table (1): Age distribution in the addicts and the control groups

Age (years)	Addicts (No. =50)	Control (No. =50)	t-test	P
Min – Max	20 – 30	20 – 30	0.83	0.40
Mean ± SD	25.46 + 2.65	24.98 + 3.09		

t: for independent t- test ***: Statistically significant at P ≤ 0.05**

Table (2): Employment distribution among the addicts and the control groups

Employment		Addicts (No. =50)	Control (No. =50)	Total	X^2 P value
Yes	**No.**	12	22	34	X^2 = 4.54 P =0.035*
	%	24.0%	44.0%	34.0%	
No	**No.**	38	28	66	
	%	76.0%	56.0%	66.0%	

χ^2: Chi square test ***: Statistically significant at P ≤ 0.05**

Table (3): Educational level among the addicts and the control groups

Educational level		Addicts (No. =50)	Control (No. =50)	Total	X^2 P value
Primary School	No.	13	10	23	
	%	26.0%	20.0%	23.0%	
Preparatory School	No.	10	7	17	
	%	20.0%	14.0%	17.0%	X^2 = 2.11
Institute	No.	15	16	31	P =0.71
	%	30.0%	32.0%	31.0%	
University	No.	12	17	29	
	%	24.0%	34.0%	29.0%	

χ^2: Chi square test ***: Statistically significant at P ≤ 0.05**

Table (4): Residence distribution among the addicts and the control groups

Residence		Addicts (No. =50)	Control (No. =50)	Total	X^2 P value
Urban	No.	35	39	74	X^2 = 0.83
	%	70.0%	78.0%	74.0%	P =0.36
Rural	No.	15	11	26	
	%	30.0%	22.0%	26.0%	

χ^2: Chi square test ***: Statistically significant at P ≤ 0.05**

Table (5): Marital status among the addicts and the control groups

Marital status		Addicts (No. =50)	Control (No. =50)	Total	X^2 P value
Married	No.	27	40	67	X^2 = 5.87
	%	54.0%	80.0%	67.0%	P =0.015*
Divorced	No.	20	8	28	
	%	40.0%	16.0%	28.0%	
Widow	No.	3	2	5	
	%	6%	4%	5%	

χ^2: Chi-square test ***: Statistically significant at P ≤ 0.05**

Table (6): Smoking index distribution among the addicts and the control groups

Smoking index	Addicts (No. = 50)	Control (No. = 50)	t-test	P
Min – Max	100 – 500	20 - 360	5.89	0.001*
Mean ± SD	300.10 + 122.94	160.00 +114.58		

t: for independent t- test ***: Statistically significant at P ≤ 0.05**

Table (7): Prolactin levels among the addicts and the control groups

	Type of case	Addicts (No. = 50)	Control (No. = 50)	t-test	P value
Prolactin	Min – Max	15 – 99	18 – 29	6.968	0.001*
	Mean ± SD	39.84 ± 25.26	14.32 ± 5.67		

t: for independent t- test ***: Statistically significant at P ≤ 0.05**

Table (8): Luteinizing hormone (LH) level among the addicts and the control groups

	Type of case	Addicts (No. = 50)	Control (No. = 50)	t-test	P value
Luteinizing hormone (LH)	Min – Max	0.25 – 5.0	0.5 – 9.5	10.766	0.001*
	Mean ± SD	1.43 ± 1.31	5.05 ± 1.85		

t: for independent t- test ***: Statistically significant at P ≤ 0.05**

Table (9): Follicular stimulating hormone level among the addicts and the control groups

	Type of case	Addicts (No. = 50)	Control (No. = 50)	t-test	P value
Follicular stimulating hormone (FSH)	Min – Max	0.2 – 9.0	2.5 – 9	4.811	0.001*
	Mean ± SD	3.56 ± 3.00	5.97 ± 1.85		

t: for independent t- test ***: Statistically significant at P ≤ 0.05**

Table (10): Estradiol level among the addicts and the control groups

	Type of case	Addicts (No. = 50)	Control (No. = 50)	t-test	P value
Estradiol	**Min – Max**	**5.8 – 71.1**	**28.6 – 75**	**6.791**	**0.001***
	Mean ± SD	**29.70 ± 20.88**	**53.40 ± 13.25**		

t: for independent t- test *: Statistically significant at P ≤ 0.05

Table (11): Total Testosterone level among the addicts and the control groups

	Type of case	Addicts (No. = 50)	Control (No. = 50)	t-test	P value
Total Testosterone	**Min – Max**	**45 – 450**	**160 – 355**	**7.364**	**0.001***
	Mean ± SD	**138.56 ± 86.33**	**246.55 ± 57.2507**		

t: for independent t- test *: Statistically significant at P ≤ 0.05