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Examination of Sexual Hormone Levels of the Hypothalamus-Pituitary - Gonad Axis and the Influence of Methadone Dose in the Treatment of Chinese Heroin Addicts

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Abstract

Background: *Sexual function decline in male heroin addicts during methadone maintenance treatment (MMT) is a problem, and the link between methadone doses and sex hormone levels in this group is unclear. This cross - sectional study explored HPG axis hormone levels and their association with methadone doses in Chinese MMT - treated heroin addicts.*

Methods: *All participants provided blood samples. Sexual hormones, including testosterone (T), progesterone (P), prolactin (PRL), follicle - stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2), were measured using radioimmunoassay (RIA). The relationship between different methadone doses ("<=30 mg/d", "31 - 60mg/d", and ">=61mg/d") and sex hormones was analyzed via general linear modeling (GLM).*

Results: *The study included 103 male heroin addicts receiving methadone maintenance treatment (MMT) and 79 healthy male controls. No significant differences were found in the levels of all sex hormones among different methadone doses (all P>0.05). After adjusting for age and the duration of MMT, no significant associations were detected between different methadone doses and the six hormone levels.*

Conclusions: *No dose - response relationship was observed for the six hormone levels. The significance of considering the independence of methadone dose effects on the HPG axis hormone levels of heroin addicts in MMT should be carefully evaluated.*

Keywords: Methadone Dose; Hypothalamus - Pituitary - Gonad Axis; Male; Heroin Addicts; China

Introduction

Since the initiation of a methadone maintenance treatment (MMT) pilot program in China in February 2003, it has achieved remarkable outcomes in preventing HIV/AIDS and reducing drug - related harms in recent years. However, several issues remain in practical implementation. For example, how to address the sexual function decline in male heroin addicts is a pressing concern. Previous studies have indicated that the prevalence of sexual dysfunction is higher in the methadone - maintained population compared to the general population [2, 3]. Sexual dysfunction is a common complaint among drug abusers, and its resolution is crucial for MMT patients to adhere to treatment and lead a normal life. The stability of the hypothalamus-pituitary-gonad (HPG) axis is essential for normal physiological

function, and the sex hormones secreted by the HPG axis play a vital role in maintaining and regulating body functions [4-8]. The restoration of sexual function in heroin addicts after detoxification is significant for reducing relapse rates and facilitating their reintegration into society. Nevertheless, some studies suggest that opiate drugs may directly suppress the pituitary gland and testicles [5, 7]. Given the lack of knowledge regarding the sex hormone levels of male heroin addicts during MMT, the first objective of this study was to measure the concentrations of testosterone, progesterone, estradiol, luteinizing hormone, follicle-stimulating hormone, and prolactin in both heroin addicts and healthy men.

Multiple factors have been proposed to influence the response to methadone maintenance treatment (MMT) [9]. Among these, the dosage is considered a critical factor [10-13]. However, determining an appropriate and optimal methadone dose remains a significant challenge [14]. Crowley reported that high methadone doses could significantly decrease the frequencies of male sexual behaviors. Kreek's research showed that the hormone levels of the hypothalamus - pituitary - gonad (HPG) axis would return to normal as libido normalized [[15,16]. Thus, we hypothesized that the underlying cause of sexual dysfunction in heroin addicts might be related to changes in sex hormones. Since the impact of methadone doses on sex hormones and the potential association between them were unknown, the second objective of this study was to explore the relationship between methadone doses and HPG axis hormones in male heroin addicts undergoing MMT. Considering the scarcity of relevant studies in China, we conducted a two - group, cross - sectional study. This research is expected to assist MMT practitioners and professionals in initiating treatment with appropriate methadone doses and, more importantly, promoting the recovery of MMT patients.

Methods

Samples

The survey was conducted from November 2024 to January 2025. A consecutive sample of 103 male heroin addicts receiving stable-dose methadone maintenance treatment (MMT) in Xi'an City, Shaanxi Province, was recruited. The inclusion criteria were as follows: (1) meeting the DSM - IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; American Psychiatric Association, 1994b) criteria for opiate dependence; (2) being male and 18 years old or older; (3) currently receiving MMT for more than 1 month; (4) willing to sign an informed consent agreement; (5) being able to comply with the study protocol; and (6) not taking medications such as antidepressants or corticosteroids. The exclusion criteria were: (1) inability to identify the primary drug of abuse; (2) having severe psychotic disorders; (3) suffering from severe physical diseases (e.g., liver or kidney diseases, prostate problems); and (4) having language or comprehensive cognitive deficits. For the control group, the inclusion criteria were: (1) being healthy male individuals; (2) aged 18 years or above; (3) having no history of drug abuse and showing no evidence of drug abuse during the study; and (4) being able to provide written informed consent. The main reasons for refusal to participate were: (1) having severe psychiatric diseases (e.g., obsessive - compulsive disorder, amnesia, or schizophrenia); (2) suffering from severe physical diseases (e.g., liver or kidney diseases, prostate problems); and (3) having recent or remote memory impairments. Ultimately, 79 cases were eligible for the control group.

Data Collection and Measures

This study was a cross-sectional survey. Prior to the formal investigation, a pilot study was conducted. The researchers involved in the survey were trained by experienced experts in specific survey techniques. Each participant was briefly informed about the research objectives to obtain their support and cooperation, after which written informed consent was obtained from all participants. A questionnaire with detailed baseline variables was provided by the National Institute on Drug Dependence, Peking University. Current socio-demographic characteristics and substance use histories were collected through face - to - face interviews. All completed questionnaires were reviewed by researchers for completeness and consistency. Incomplete or inconsistent questionnaires were excluded from the final analysis.

Subjects in the MMT were not randomly assigned to a specific dose level; the decision to increase or decrease the maintenance dosage was made by the attending doctor. Each participant was assigned a study serial number, which they were asked to record in the signature file. Blood specimens were collected before breakfast. Five milliliters of venous blood were drawn into non - gel - top tubes and allowed to clot spontaneously at room temperature for 30 minutes. After centrifugation at 4000 rpm for 8 minutes, serum was collected. The samples were then divided into two 1-ml tubes and immediately frozen at below - 20°C. All assays were performed in one batch upon the completion of the study. Sexual hormones, including testosterone (T), progesterone (P), prolactin (PRL), follicle - stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2), were measured using radioimmunoassay (RIA). The intra - assay coefficients of variation for the hormone measurements using the reagent kits were all less than 10.0%, and the inter - assay coefficients of variation were all less than 15.0%.

Statistical Analysis

During the study's observation period, the methadone doses of the participants ranged from 6 mg to 110 mg per day, with a mean dose of (47.7 ± 23.40 mg/d) and a median dose of 40.0 mg/d. Nearly half of the participants (49.0%) took a dosage between 31-60mg/d, approximately 30% took a dosage of <=30mg/d, and 21.6% took a dosage higher than 60 mg daily. Based on the actual methadone administration levels in China and Blaney's study, the methadone-maintained patients were classified into three groups according to their daily dose levels: a low - dose group (≤30 mg/d), a medium - dose group (31-60mg/d), and a high - dose group (≥61mg/d) [17]. The healthy controls were designated as the no - dose group. Statistical analysis was performed using SPSS software for Microsoft Windows. Quantitative variables with a symmetric distribution were described by the mean and standard deviation, while those with a skewed distribution were described by the median. Non-parametric statistical tests were employed when the distribution was non-normal. Descriptive statistics were used to analyze the distributions of demographic characteristics and hormone levels. One-way analysis of variance (ANOVA) or the Chi - Square test was used to explore differences among the three methadone - dose groups. The Kruskal-Wallis H test was applied to investigate potential differences in each HPG axis hormone level across groups. Additionally,

general linear modeling (GLM) was utilized to examine the association between HPG axis sex hormone levels and different methadone doses (≤30 mg/d, 31-60 mg/d, and ≥61 mg/d).

Potential confounding factors in this study included the subjects' age and the duration of MMT. Notably, significant differences in the duration of MMT were observed among different dose groups. Therefore, age and the duration of MMT were adjusted for in the actual analysis. All statistical significance tests were two - tailed, with an alpha level of 0.05.

Ethics Consideration

Before the interviews and blood sampling, participants were informed about the study's purpose, and their consent to participate was obtained. The survey procedures were designed to protect participants' privacy through anonymity. Participants had the right to withdraw from the study at any time. The study was approved by the Ethical Committee of Peking University Health Center (Grant No. IRB00001052 - 10026). ##

Results

Baseline Data of Study Participants from Three Methadone-Dose Groups

The age of the 103 MMT individuals ranged from 20 to 52 years, with a mean age of 39.5±6.8 years. The participants in this study had diverse educational backgrounds and marital statuses. Most (66.0%) had a junior high school education or lower, and only 1.0% had a university - level education. Among the total samples, over half (60.8%) were married. The mean age of the 79 healthy men was 32.8 years (standard deviation, SD = 9.8), with an age range of 19 to 55 years. Overall, there were no significant differences in dose among the three groups (P > 0.05). The subjects' age, education, marital status, and duration of methadone maintenance treatment (MMT) across different methadone - dose groups are presented in Table 1. The distributions of age, educational level, and marital status did not differ significantly among the different methadone doses. However, the duration of MMT differed significantly among the three dose groups (P < 0.001).

Table 1: General Characteristic of Study Participants by Dose Category

Variables	Any doses (n=103)	Low dose (<=30mg/d) (n=30)	Medium dose (31-60mg/d) (n=50)	High dose (>=61mg/d) (n=22)	F/x^2	P
Age(year)						
Mean ± SD	39.5±6.8	39.7±6.10	38.8±7.24	41.6±5.81	1.353*	0.263
Range	20-52	20-48	20-49	21-52		
Education						
Primary school and below	15(15.0)	5(17.2)	5(10.0)	5(23.8)	0.180**	0.151
Junior high school	52(51.0)	19(65.5)	22(44.0)	10(47.6)		
Senior high school	33(33.0)	5(17.2)	22(44.0)	6(28.6)		
University	1(1.0)	0(0)	1(2.0)	0(0)		
Marital status						
Married	62(60.8)	19(63.3)	27(54.0)	16(72.7)	0.307**	0.299
Others	40(39.2)	11(36.7)	23(46.0)	6(27.3)		
Duration of MMT (month)						
Mean ± SD*	18.1±11.91	15.3±8.66	15.8±9.59	27.0±15.97	9.120*	<0.001
Range	1-49	1-36	1-39	2-49		

Note. *One-way analysis of variance (ANOVA) ** Chi-Square test

Trends in Hormone Levels of the HPG Axis by Three Different Methadone Doses

As shown in Table 2, no significant differences were detected in the hormone levels of the hypothalamus - pituitary - gonad (HPG) axis among different methadone doses (all P > 0.05). When compared with the healthy controls, significant differences were found in all six hormones in the "<=30 mg/d" group (P<0.05); in the "31 - 60 mg/d" group, significant differences were observed in five hormones except testosterone (T) (P<0.05); and in the ">=61 mg/d" group, only the levels of T and progesterone (P) differed significantly from those of the healthy controls (P<0.05). When comparing each sex hormone, the T levels in the low - and high - methadone - dose groups were higher than those in the healthy controls (P<0.05); the P levels in all three dose groups were lower than those in the controls (P<0.05); the prolactin (PRL) and luteinizing hormone (LH) levels in the low - and medium - methadone - dose groups were higher than those in the controls (P<0.05), while the follicle - stimulating hormone (FSH) and estradiol (E2) levels in the low - and medium - methadone - dose groups were lower than those in the controls (P<0.05). The Kruskal - Wallis H test indicated no significant differences in sex hormones among the three methadone - dose groups (P > 0.05). However, after adjusting for age and the duration of MMT, the trends in sex hormone levels with different methadone doses became notable (see Figure 1). In particular, the levels of T, P, FSH, and LH exhibited a biphasic change pattern in individuals treated with different methadone doses. Conversely, PRL levels decreased and E2 levels increased with increasing methadone doses.

Table 2 Comparison and association of different methadone doses with hormone levels of HPG axis

		T(ng/ml)	P(ng/ml)	PRL(ng/ml)	FSH(mIU/ml)	LH(mIU/ml)	E2(pg/ml)
No dose	N(missing*)	78	79	75	75	73	78
(n=79)	Median	8.35●	1.51	6.78	9.43	6.63	18.20
	Min-Max	(6.32-9.42)	(1.51-8.91)	(2.79-26.21)	(1.59-22.75)	(2.51-16.85)	(4.96-48.15)
<=30 mg/d	N(missing*)	20	15	23	24	28	28
(n =30)	Median	10.48●	0.59●	8.89●	5.95●	8.31●	12.50●
	Min-Max	(3.00-13.89)	(0.08-4.45)	(5.80-41.15)	(2.68-29.77)	(3.08-24.04)	(6.70-39.19)
31-60 mg/d	N(missing*)	39	24	43	37	48	42
(n =50)	Median	8.25	0.37●	8.11●	7.08●	9.04●	14.29●
	Min-Max	(3.49-13.89)	(0.04-5.93)	(3.22-49.14)	(2.50-17.68)	(2.72-17.62)	(6.15-32.44)
>=61 mg/d	N(missing*)	16	15	16	17	22	21
(n =22)	Median	9.90	0.79●	7.73	9.53	8.23	12.67
	Min-Max	(3.53-13.01)	(0.04-3.88)	(3.09-22.78)	(2.37-15.86)	(4.80-13.75)	(6.59-68.86)
Chi-Square**	3.482	0.560	1.635	2.783	1.278	0.621	
P	0.175	0.756	0.442	0.249	0.528	0.733	

Note.* Because of some specimens could not achieve the standard of assay.

** Kruskal-Wallis H test was used for comparison between different doses of MMT groups (<=30 mg/d, 31-60 mg/d and >=61 mg/d)

- Kruskal-Wallis H- test was used for comparison between healthy controls and three different doses of MMT groups.
- Contrast to "no doses group", P<0.05;

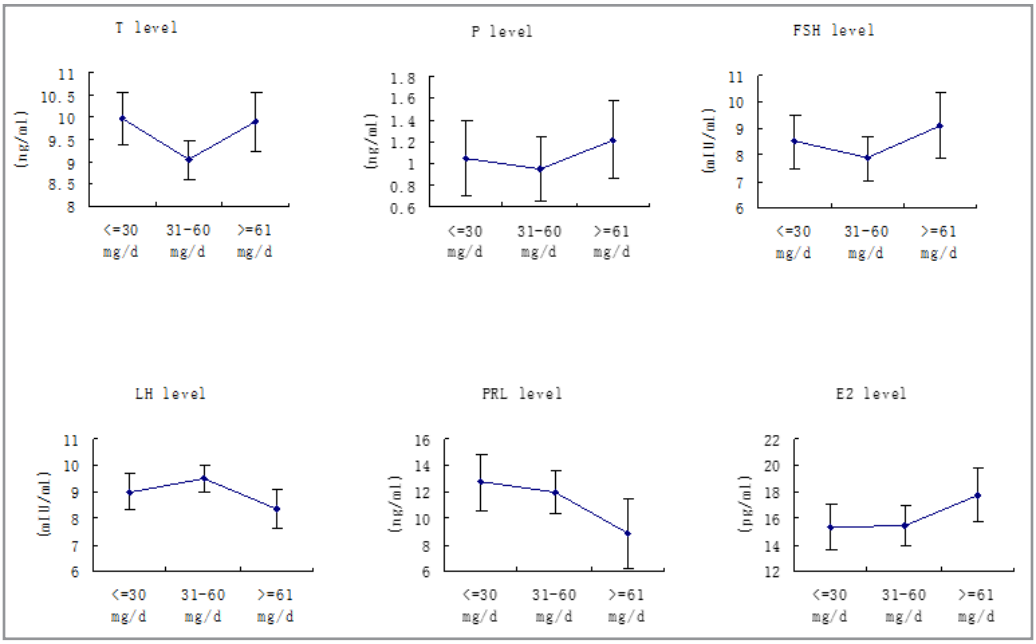

Figure 1: Adjusted Means and Standard Errors For T, P, Fsh, Lh, Prl And E2 Levels by Three Different Doses of Methadone (Adjustment for Age of Subjects and Duration of MMT).

Relationship between Methadone Doses and Hormone Levels of the HPG Axis

To account for confounding factors, general linear modeling (GLM) was used to examine the association between different methadone doses (≤30 mg/d, 31 - 60 mg/d, and ≥61 mg/d) and sex hormone levels, with age and the duration of MMT as adjusted variables. Table 3 shows that the interaction between variables and intercepts did not differ significantly among the three dose groups (P > 0.05), indicating that further association analysis was feasible. As presented in Table 4, GLM analysis revealed that the association between the three methadone doses and all sex hormone levels did not reach statistical significance (P > 0.05).

Table 3 Analysis for interaction of variables and tests of between subjects effects

Levels of hormones	Age of subjects		Duration of MMT		Dose of methadone		Dose*duration in MMT	
	F*	P	F*	P	F*	P	F*	P
T	0.012	0.914	0.004	0.949	0.738	0.482	1.315	0.275
P	0.372	0.545	0.562	0.457	0.416	0.662	0.472	0.627
FSH	0.958	0.331	2.303	0.134	0.207	0.814	0.403	0.670
LH	0.973	0.326	0.797	0.375	0.070	0.932	0.258	0.773
PRL	0.291	0.591	0.076	0.783	0.192	0.826	0.295	0.745
E2	0.146	0.704	1.221	0.272	1.471	0.236	2.150	0.123

Note.* General linear modeling (GLM) was used for analysis for interaction of variables and tests of between subjects effects.

Table 4: Relationship Between Sex Hormones Level and Daily Methadone Dosage

	F*	P
T	1.230	0.299
P	0.249	0.780
FSH	0.287	0.752
LH	0.755	0.473
PRL	0.620	0.541
E2	0.310	0.735

Note. * General linear modeling (GLM) was used to examine the association between three different doses of methadone (<=30 mg/d, 31-60 mg/d and >=61 mg/d) and all sex hormone levels of HPG after adjusting for age of subjects and duration of MMT.

Discussion

This study demonstrated that the sexual hormone levels of heroin addicts receiving methadone treatment differed from those of healthy men, and there were also differences in sex hormone levels among the three methadone-dose groups. Moreover, different methadone treatment doses were not associated with sex hormone secretion.

In the present study, no association was found between sex hormone levels and methadone doses in male heroin addicts undergoing methadone maintenance treatment (MMT). For instance, testosterone (T) levels were not correlated with different methadone doses ($F = 1.230$, $P = 0.299$), which is consistent with some previous studies [18, 19]. Additionally, this study did not detect an association between different methadone doses and luteinizing hormone (LH) ($F = 0.755$, $P = 0.473$) or follicle - stimulating hormone (FSH) ($F = 0.287$, $P = 0.752$). Furthermore, the results did not support the hypothesis that methadone dose had a significant effect on progesterone (P) ($F = 0.249$, $P = 0.780$), prolactin (PRL) ($F = 0.620$, $P = 0.541$), and estradiol (E2) ($F = 0.310$, $P = 0.735$). Overall, there were no significant differences between methadone doses and sex hormone levels, suggesting that the appropriate dose for an individual may be more crucial than the categorization of low, medium, or high doses [20]. Rose found that a daily methadone dose of 130 mg caused severe erectile dysfunction (ED), while an individual's sexual function recovered after switching to a 40 - mg daily dose, and the serum LH and FSH concentrations returned to normal [21]. In our study, only 21.6% of the subjects took a dosage higher than 60 mg daily, which was considered a high methadone dose. Thus, for the Chinese drug-using population in this survey, tolerance to the opiate - induced suppression of pituitary gonad hormones may have developed. However, our findings should be interpreted with caution because in drug-using populations, HPG axis dysfunction is influenced by multiple factors, including the direct effects of drugs and the indirect effects of other factors [22-25].

This study found that the testosterone (T) level in methadone - maintained cases was higher than that in healthy controls, which contradicts some previous studies showing reduced T levels in opiate addicts [26, 27] and in men using methadone [28-32]. Several possible explanations exist for these differences. Firstly, the rehabilitation of pituitary function depends on the regulation of the central nervous system (CNS) and hypothalamus (LH). In our study, the function of the CNS and the regulation of LH disrupted by opiates may have gradually recovered under methadone treatment. Secondly, the increased secretion of LH may be a contributing factor to the elevated T levels. It is known that serum T can regulate the synthesis and secretion of serum LH through a feedback mechanism, and elevated LH stimulates Leydig cells, leading to an increase in serum T concentrations [33]. Thirdly, opiate drugs can inhibit PRL secretion, which has a negative feedback effect on LH release [34]. Therefore, we concluded that the inhibited PRL may affect the negative feedback of T release.

In this investigation, no significant differences were found between sex hormone levels and methadone doses, and over half (57.8%) of the participants had been in methadone maintenance treatment (MMT) for more than 12 months. Thus, it can be tentatively concluded that long-term methadone-maintenance treatment may not have a restorative effect on the HPG axis. The inhibition of the HPG axis may be mainly attributed to the long - term history of heroin addiction.

These findings should be interpreted in the context of the following limitations. First, this study was unable to obtain the blood specimens of the samples prior to their enrollment in methadone

maintenance treatment (MMT). Consequently, we were unable to establish the baseline hormone levels and lacked the means to closely monitor the dynamic changes in hormone levels during MMT. Second, in the present survey, only healthy men were selected as the control group. To expand the scope of our observations, it is necessary to examine the hormone levels of male heroin addicts who are not undergoing methadone therapy. Third, the use of convenience sampling limited the representative of the sample. Given that drug abuse is a highly sensitive issue, randomly sampling a hidden population with sensitive parameters is challenging. Our sample was composed of middle - aged individuals (mean age = 39.5 ± 6.8) with relatively low educational attainment, as 66.4% had less than a junior high school education. Fourth, the hypothalamus - pituitary - gonad (HPG) axis is highly sensitive to various internal and external factors. Stress, depression, gender, seasonal variations, and medications are among the many factors that can influence the HPG axis and its sensitivity. In this study, the investigation was conducted in a stable environment, and only male addicts were surveyed. Individuals with depression and a history of taking medications such as antidepressants or corticosteroids were excluded. However, the potential interactions of hormone levels with other illicit drugs, poly - drug use, alcohol, and seasonal factors were not statistically evaluated. These aspects should be explored in future studies and considered in clinical applications.

In conclusion, this study offers a basic understanding of the relationship between methadone treatment dosages and sex hormones. Given the variations in sex hormone levels across different methadone doses, additional research is essential before making any medical recommendations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors contributions

ZM Liu conceived and planned the study. HR. Zhang carried out the statistical analyses, drafted the manuscrip. All authors read and approved the final manuscript.

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Data availability

Data will be made available on request.

Highlights

1. Sex hormone levels differed between male heroin addicts on MMT and healthy men.
2. No significant link between methadone doses and sex hormones was found.
3. The significance of methadone dose - HPG axis hormone independence in MMT - treated heroin addicts needs careful evaluation.

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