

EJACULATION DISORDERS

Novel Marker for Premature Ejaculation: Serum Leptin Level



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ABSTRACT

Background: Leptin, which was only discovered in humans in 1994, has recently been shown to have a possible link with premature ejaculation.

Aim: To evaluate whether serum leptin levels differed between patients with premature ejaculation and healthy men, and to analyze the changes in leptin levels before and after treatment.

Methods: Six studies assessing the relationship between leptin and premature ejaculation published up to October 2021 were identified from multiple databases (PubMed, Web of Science, Cochrane) and the data were analyzed by Stata software.

Outcomes: Differences in leptin levels in premature ejaculation patients and healthy people, and changes of leptin levels in premature ejaculation population before and after treatment.

Results: Analysis of studies assessing differences in leptin concentrations between patients with PE and healthy men showed that there was a statistically significant difference in leptin levels between PE patients and controls (WMD (95% CI) = 17.89 (8.64, 27.14), $P < .001$). On the other hand, the analysis of data from 3 studies describing serum leptin levels in PE patients before and after treatment with selective serotonin reuptake inhibitors (SSRIs) showed that there was a significant decrease with leptin levels in PE patients after treatment (WMD (95%CI) = 22.06 (17.21, 26.92), $P < .001$).

Clinical Implications: It is possible that leptin can be used as a new marker for premature ejaculation.

Strength & Limitations: The strength of this study is that it is the first meta-analysis to assess the differences of serum leptin levels between patients with premature ejaculation and healthy subjects and the changes of leptin levels before and after treatment in patients with premature ejaculation. A major limitation is that a greater heterogeneity was identified through our analysis, however we did not find a definitive source of heterogeneity.

Conclusion: There was a statistically significant relationship between serum leptin levels and patients with PE. In addition, serum leptin levels in patients with PE decreased significantly after 8 weeks of treatment with SSRIs.

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Key Words: Leptin; Premature Ejaculation; Meta-Analysis; Intravaginal Ejaculatory Latency Time; Selective Serotonin Reuptake Inhibitors

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INTRODUCTION

Clinical premature ejaculation (PE) is thought to occur in about 5% of the adult male population.¹ As a common male disease, PE can potentially affect a man's life in many ways, such as damaging self-esteem, anxiety, depression, and may even endanger the stability and harmony of the family. The subjective of PE makes it difficult to have a conclusive definition. However, many several scientific societies and scholars provided different definitions of PE according to different situations, such as time of onset and pathogenesis.²

Although PE is considered to be the most common sexual dysfunction in men, its etiology remains uncertain. While it was previously considered that PE was only a psychological problem, research in recent years has shown that PE can be affected by a variety of physical, genetic and neurobiological disorders.³ Moreover, factors such as chronic prostatitis, hyperthyroidism, metabolic syndrome and erectile dysfunction (ED) are also associated with PE,⁴⁻⁷ and this is 1 of the reasons why PE is so difficult to fully understand and classify. Precisely because of its complexity and uncertainty, premature ejaculation has attracted increasing research interest.

Several studies have proposed the pathogenesis of primary PE (PPE) in terms of neurobiology, such as the 5- hydroxytryptamine hypothesis, which suggests that 5- hydroxytryptamine (5-HT) inhibits ejaculation and reduces glans sensitivity, so, dysfunction of 5- hydroxytryptamine neurotransmitters may contribute to PPE.⁸⁻¹⁰ Leptin is a fat cell-derived hormone discovered by Zhang et al. in 1994 which plays a key role in regulating energy intake and energy expenditure by signaling to the hypothalamus about food intake, the regulation of weight, and sexual behavior.^{11,12} Leptin has been extensively studied since its discovery, several studies have demonstrated that changes in leptin levels are associated with coronary atherosclerosis,¹³ breast carcinoma,¹⁴ chronic heart failure,¹⁵ etc. In addition, more and more studies have focused on the leptin levels in the various psychiatric disorders recently,¹⁶ and several studies have shown that leptin can reduce the serum 5-HT levels or inhibit its effects, which is associated with PE.¹⁷⁻¹⁹

However, the samples of these studies were small, making the conclusions lack some credibility. Therefore, we conducted he systematic review and meta-analysis to illustrate the problem more convincingly by combining these studies. To the best of our knowledge, to date, this is the first meta-analysis to explore the relationship between leptin and PE. Our main purpose of this meta- analysis was to investigate the following questions: (i) Are there really differences in serum leptin levels between PE patients and healthy individuals; (ii) do leptin levels in PE patients change if they have received first-line treatment?

METHODS

To ensure that the current standard for meta- analysis methodology was met, our meta- analysis was performed according to

the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).²⁰ The approval from the Medical Ethics Committee was unrequired in our meta- analysis it did not involve any ethical issues.

Literature Search Strategy

We performed an extensive systematic search on PubMed, Web of Science, and Cochrane Library to access all relevant published up to October 30, 2021 without any restrictions. The search terms used were as follows words: (“premature ejaculation” [Medical Subject Headings] OR “premature” [All Fields] AND “leptin” [MeSH] OR “leptin” [All Fields]. After obtaining the preliminary database search, we scanned the title, abstract and full text of the articles to assess whether they accord with our preset inclusion criteria, and excluded relevant studies based on the exclusion criteria. Then the papers included were retained for data extraction after full text review. The literature searching process was performed by 2 of the authors (Guodong Liu, Yuyang Zhang) independently and any case of disagreement was resolved with discussion until consensus was reached.

Inclusion and Exclusion Criteria

Criteria for selecting the subjects were as follows: (i) comparing serum leptin levels in patients with premature ejaculation and healthy controls; (ii) evaluating changes of serum leptin levels before and after treatment with SSRIs in patients with premature ejaculation; (iii) using a validated instrument for diagnostic of PE such as IELT, the Index of Premature Ejaculation. Studies meeting any of the following criteria were excluded: (i) studies lacking the necessary statistical data, such as variance; (ii) studies written in a language other than English; (iii) the types of studies were reviews, animal experiments, comments, case reports, or letters.

Data Extraction and Quality Assessment

The data for the meta- analysis were fetched from the original studies by 2 independent reviewers (Liu and Zhang) through a predesigned form. The following details were extracted: characteristics (the name of the author, the year and location of publication, number of patients group and the control) and results (serum leptin levels) of the study. Additional data collection is required (serum leptin levels of baseline and after treatment) if the study involved comparing serum leptin levels of PE patients before and after SSRIs treatment. In our meta- analysis, the quality of studies was assessed using the Newcastle- Ottawa Scale (NOS) (scores ≥ 5 indicating moderate- high quality and < 5 indicating low- quality studies).²¹

Outcome Assessment and Statistical Analysis

Our meta- analysis consisted of 2 parts. Firstly, we compared serum leptin levels between patients with PE and healthy controls. Another result of our meta- analysis was to evaluate changes

of serum leptin levels before and after treatment with SSRIs in patients with premature ejaculation. We calculated the Weighted Mean Difference (WMD) and corresponding 95% confidence intervals (95% CIs) to evaluate the relationship between these data. Besides, Statistical heterogeneity was estimated using I square test (I^2) and Cochran's Q test.²² Due to intra and inter-study variability, which can lead to a high degree of heterogeneity in meta- analyses, we selected the random- effects model for analysis when heterogeneity was high ($I^2 > 50\%$ or $P < .050$). In addition, we performed subgroup analyses to try to find sources of heterogeneity and we conducted a sensitivity analysis in order to assess the stability of the combined results, which allows the impact of individual studies to be measured by excluding each study individually. Finally, we performed funnel plots and Egger's test to evaluate any possible publication bias, and there will exist positive publication bias when a value ' $P > |t|$ ' below .05 of the Egger's test. All statistical analyses were conducted using Stata software (version 16; Stata Corporation, College Station, TX, USA). P values $< .05$ were considered statistically significant.

RESULTS

Study Characteristics

In our meta- analysis, the search resulted in a total of 20 references (8 articles from PubMed, 10 from Web of Science, and 2 from Cochrane Library). After the excluding duplicate items by EndNote software (version X9.1; Thomson Corporation, Stamford, CT, USA), the resulting list comprised 12 potentially relevant articles. Of these, 6 studies were retained finally in our meta- analysis after we reading the full text carefully, which accord with all of inclusion criteria (5 studies compared serum leptin levels in the PE patient group and the control group; 3 of these studies analyzed leptin levels in PE patients before and after treatment with SSRIs).^{17-19,23-25} The detailed process is listed in [Figure 1](#). The main characteristics of selected studies are shown in [Table 1](#) and [Table 2](#). In addition, the NOS scores of the selected researches ranged between 7 and 8, which meant the studies we selected are reliable ([Table 3](#)).

Serum Leptin Levels in PE Patients and Healthy Controls

In 5 studies on the relationship between leptin and premature ejaculation, a total of 285 PE patients and 269 healthy controls were included. The forest plot comparing the leptin levels between 2 groups was shown in [Figure 2](#). WMD was calculated to compare leptin levels between PE patients and healthy controls. The results manifested that the leptin levels in PE patients was approximately 17.89 ng/ml higher than controls (WMD (95% CI) = 17.89 (8.64, 27.14), $P < .001$), which means that serum leptin levels are significantly higher in PE patients compared to healthy individuals, and there was serious heterogeneity ($I^2 = 99\%$). Due to the high heterogeneity, we applied a random

effects model to calculate the WMD at 95% CI. To find the sources of heterogeneity and assess the reliability and stability of our results, we performed the following series of operation. First, we divided the studies into 3 subgroups according to their different intravaginal ejaculatory latency time (IELT) (a. IELT < 30 s, b. 30 s $< \text{IELT} < 60$ s, c. IELT > 60 s), from which, unfortunately, we did not find heterogeneous sources ([Figure 3](#)). Then we performed a sensitivity analysis, the results of which are shown in [Figure 4](#), indicating that Mohammed's study may be 1 of the causes of the high heterogeneity. In addition, we used Egger test ([Figure 5](#)) to assess publication bias and found no significant bias in our selected publications ($P = .509$). And based on the funnel plot ([Figure 6](#)), we can also clearly see that there was no significant bias in our selected studies.

Changes of the Leptin Levels in PE Patients With the SSRIs Therapy

Of the 6 studies we retrieved, 3 compared changes in leptin levels in PE patients before and after 8 weeks of treatment with moderate doses of SSRIs (50 to 60 mg/d).^{23,25,26} We performed a data analysis and the comprehensive results showed that after 8 weeks of treatment with SSRIs in patients with PE, the leptin levels of patients had decreased by 22.06 ng/ml ($I^2 = 94\%$, $P < .001$, 95% CI = 17.21, 26.92).

DISCUSSION

The study we conducted is the first meta- analysis comprehensively assess the available data regarding the relationship between leptin and PE, and result that there was a significant and meaningful increase of leptin levels in PE patients ($P < .001$). This conclusion could still be obtained after a series of statistical treatments such as heterogeneous type tests and subgroups analysis. In additional, we combined data from 3 existing studies assessing changes in leptin levels in patients with PE before and after treatment with SSRIs and concluded that serum leptin levels decreased significantly after treatment in patients with PE ($P < .001$).

PE is considered to be the most common male sexual disorder, but so far there is not a universally precise definition and diagnosis of it.²⁷ Although recent publications suggest the need for a multidimensional definition that includes the following 3 dimensions: (i) IELT, (ii) self- perceived control, (iii) negative impact on mood and life.²⁸ It has also been suggested that the underlying etiology and risk factors need to be identified along with the diagnosis of PE.²⁹ Several studies have suggested that a number of relevant routine tests should be done before diagnosing PE, such as endocrine hormones,³⁰ prostatitis,⁶ diabetes,³¹ hyperthyroidism,⁷ short frenulum³² psychosexual factors, interpersonal relationships, and several other factors,³³ which have been shown to play a potential role in PE. However, most current clinical tests still depend on the patient's subjective level of distress to reflect the severity of the underlying disease. Therefore, objective indicators of PE would be useful for clinicians. In

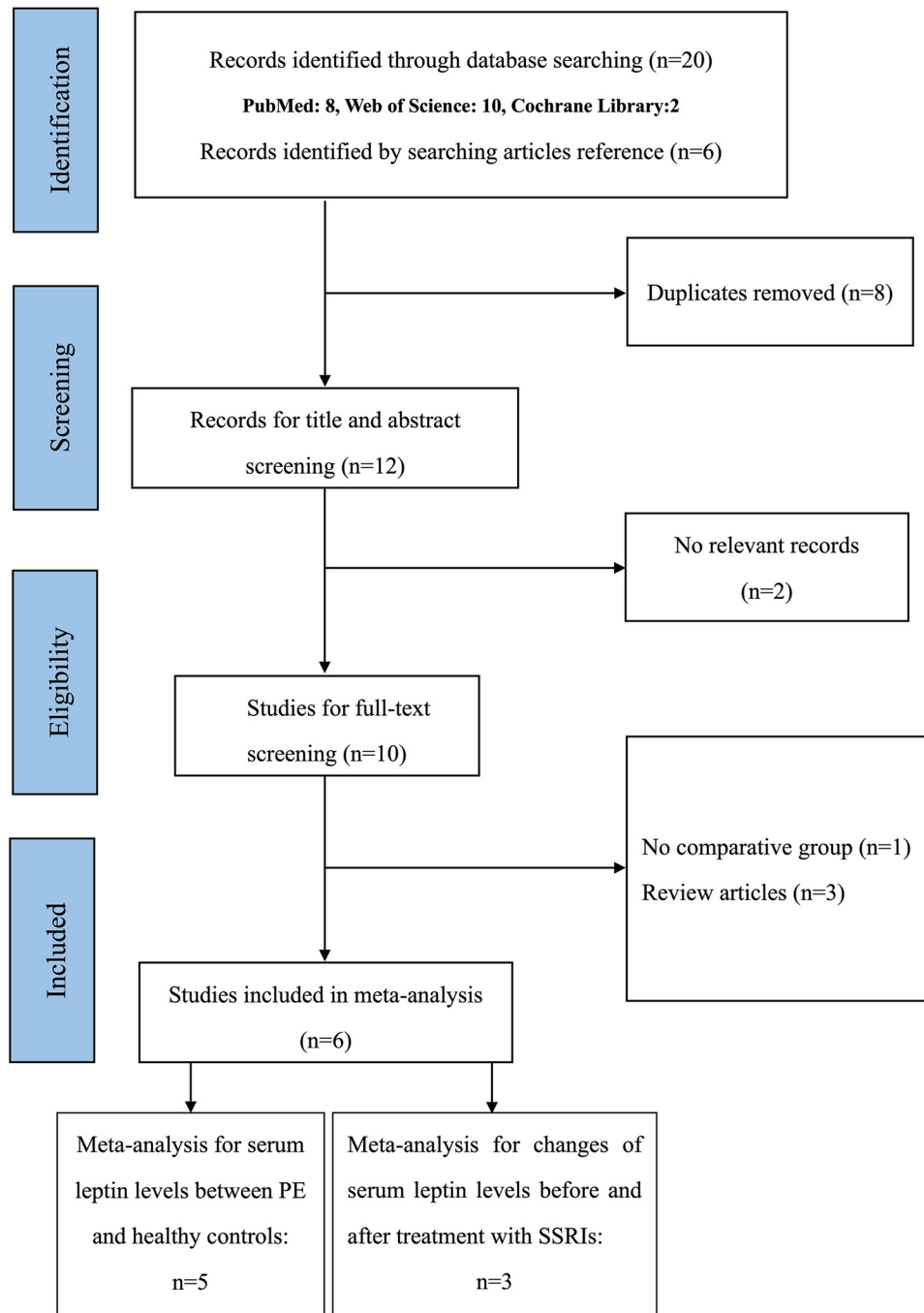


Figure 1. Flowchart of studies selection process.

recent years, some new tests such as electro neurophysiological techniques have been used to diagnose PE,³⁴ However, these techniques also still have some drawbacks: most are invasive, some are very cumbersome, require active patient cooperation, and are difficult to use in clinical practice. Simple indices that can objectively detect PE and are acceptable to the patient are urgently needed.

From a neurological aspect, ejaculation is a process of neurophysiological reflexes regulated by the complex neurophysiological mechanisms, which refers to expulsion of semen from the urethra, including emission, ejaculation and intense pleasure. A

basic study showed that the medial preoptic nucleus of the rat hypothalamus and the paraventricular nucleus of the forebrain have a crucial role in the pivotal control of ejaculation.³⁵ Nucleus paragigantocellularis (nPGi) inhibits motor neurons in the lumbosacral region through the release of 5-hydroxytryptamine and yields sustained ejaculatory inhibition via descending pathways. The 5-HT released from the nPGi inhibits lumbosacral motor neurons, producing sustained inhibition of ejaculation through a descending pathway. Rats with removed or weakened nPGi exhibit prolonged ejaculatory latency.³⁶ Therefore, it is likely that nPGi is an important component of the structures involved

Table 1. Characteristics of included studies comparing the serum leptin levels between PE patients and healthy controls

Author	Year	Country	PE Patients				Healthy controls			
			Number	Age, year	IELT, s	Serum leptin levels(ng/ml)	Number	Age, year	Serum leptin levels (ng/ml)	
Atmaca et al.	2002	Turkey	15	30.5 ± 6.2	32.3 ± 17.4	25.7 ± 3.9	15	27.7 ± 5.8	7.9 ± 2.1	
Mohammad et al.	2008	Iran	46	33.1 ± 8.3	16.7 ± 4.9	8.31 ± 3	44	31.8 ± 7.0	3.28 ± 1.4	
Kunlong Tang et al.	2013	China	108	30.27 ± 6.48	54 ± 25	32.9 ± 7.7	104	32.92 ± 7.39	8.8 ± 2.6	
Baolong Wang et al.	2013	China	59	30.27 ± 6.48	54.1 ± 31.3	32.94 ± 7.72	64	32.92 ± 7.39	8.84 ± 2.65	
Jiadong Xia et al.	2020	China	57	31.7 ± 6.1	69 ± 40.5	27.8 ± 7.1	42	31.2 ± 4.7	9.3 ± 4.3	

Table 2. Characteristics of included studies comparing the serum leptin levels in PE patients before and after treatments with SSRIs

Author	Year	Country	Number	Serum leptin levels (ng/ml)	
				Patients (before treatment)	Patients (after 8weeks treatment)
Atmaca et al.	2003	Turkey	15	23.9 ± 5.3	8.3 ± 2.8
Kunlong Tang et al.	2013	China	108	32.9 ± 7.7	8.0 ± 1.9
Baolong Wang et al.	2013	China	59	32.94 ± 7.72	7.76 ± 2.22

Table 3. Quality assessment for all the included studies

First author (Year)	Selection		Comparability				Outcome		Score	
	Case definition adequate	Representativeness of the cases	Selection of controls	Definition of controls	Main factor	Additional factor	Ascertainment of exposure	Same Method of ascertainment for cases and controls		Non-response rate
Atmaca et al. (2002)	*	*	*	*	*	*	*	*	—	8/9
Atmaca et al. (2003)	*	*	*	*	*	*	*	*	—	8/9
Nikoobakht et al. (2008)	*	*	*	—	*	*	*	*	—	7/9
Kunlong Tang et al. (2013)	*	*	*	*	*	*	*	*	—	8/9
Baolong Wang et al. (2013)	*	*	*	*	*	*	*	*	—	8/9
Jiadong Xia et al. (2020)	*	*	*	*	*	*	*	*	—	8/9

*Indicates "fulfilled" or "yes."

in the central control of ejaculation. A review detailed the possible mechanism of SSRIs for the treatment of premature ejaculation: SSRIs can inhibit 5-HT re-uptake sites on the presynaptic membrane, promote 5-HT transport, and increase 5-HT

concentration in the synaptic cleft, thereby improving ejaculatory control and delaying ejaculation.³⁷ Interestingly, since SSRIs can cause sexual side effects in the treatment of other diseases, there have been subsequent studies suggesting its role in the treatment

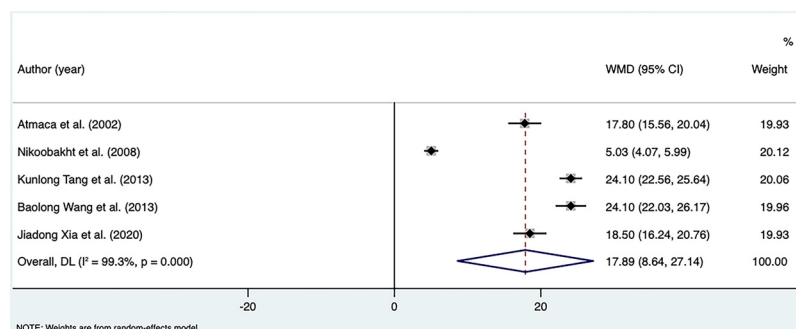


Figure 2. Forest plot for the comparison of the leptin levels between PE patients and healthy controls.

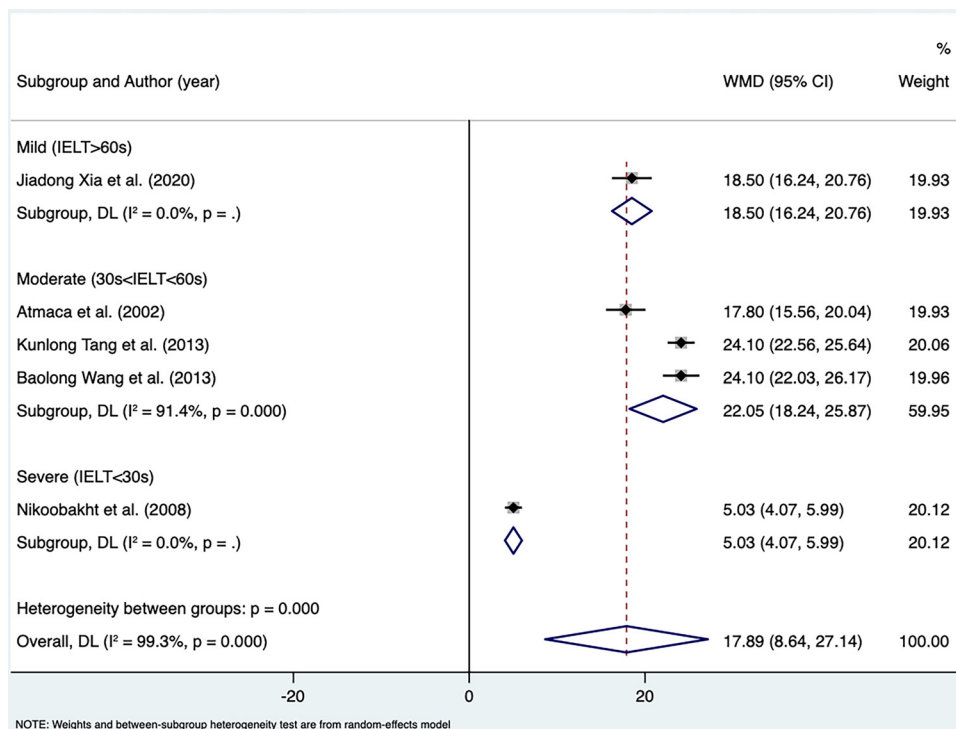


Figure 3. Subgroup analysis of the leptin levels between ED patients and healthy subjects (a. IELT < 30s, b. 30s < IELT < 60s, c. IELT > 60s).

of patients with premature ejaculation.³⁸ To date, there have been a large number of clinical researches regarding the therapy of PE with SSRIs. Not only have these studies been tremendously informative for the clinical treatment of PE, but they have also confirmed the relationship between 5-HT and PE and deepened our comprehension of the mechanisms of ejaculation regulation.³⁹⁻⁴¹

Although it is well known that sexual function is regulated to some extent by hormones, the participation of the endocrine system in the regulation of IELT is not fully appreciated.⁴² Several studies have proposed that oxytocin, prolactin, thyroid and

gonadal hormones can help control ejaculation to varying degrees, and conversely, ejaculation problems can occur with endocrine dysregulation.⁴³⁻⁴⁹ Banks et al. revealed that leptin can inhibit luteinizing hormone(LH) - stimulated testosterone release,⁵⁰ which could possibly provide a new idea for the study of premature ejaculation. We drew a flow chart of the ejaculatory process based on the relevant studies mentioned above and illustrated the role of hormones in the ejaculatory process (Figure 8).

Leptin, since its discovery in 1994, has been shown to be a hormone derived from adipocytes and has been associated with food intake, weight regulation and sexual behavior.^{11,12} In

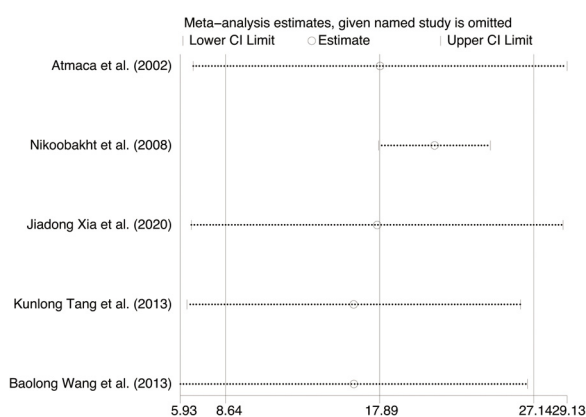


Figure 4. Sensitivity analysis of the selected studies for the level of leptin between PE patients and controls.

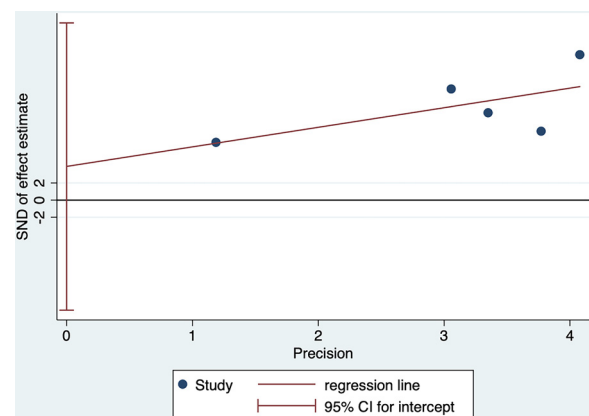


Figure 5. Egger's test plot for publication bias about serum leptin levels in PE patients before and after treatments with SSRIs.

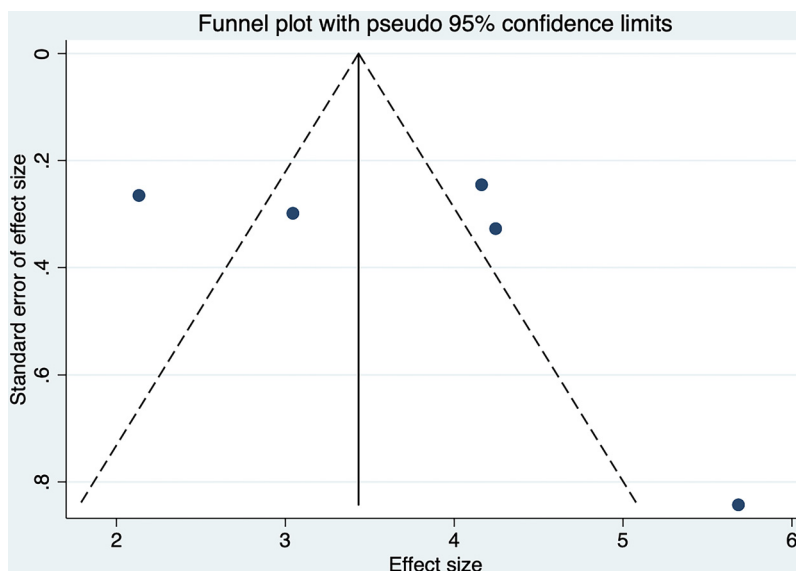


Figure 6. Funnel plot publication bias about serum leptin levels in PE patients before and after treatments with SSRIs.

addition, the inhibitory effect of 5-HT on feeding behavior in rats has been demonstrated in detailed experimental animal studies in the last century.⁵¹ Some scholars have discovered the side effects of SSRIs use on human body weight, and through research have identified a possible contribution of 5-HT to appetite and weight regulation in humans.⁵² Gamaro et al. have demonstrated in animal experiments that dosage of the SSRI drug fluoxetine significantly reduced food intake and decreased plasma leptin levels in rats.⁵³ Leptin has been found to have a biologically active free and possibly inactive form in the circulation, and obese individuals typically produce higher levels of leptin than lean individuals.⁵⁴ Furthermore, recent studies have shown that leptin is expressed abnormally in many disease conditions.⁵⁵ In addition, this protein hormone may also play a role in the regulation of sexual function. On the basis of these studies, Atmaca et al. first proposed in 2002, and verified the correlation between serum leptin levels and premature ejaculation in a cohort study, which triggered our interest as well.¹⁷

Recent studies have suggested that leptin and 5-HT may regulate each other's expression. As they found that a decreased 5-HT in rat hypothalamic tissue may contribute to the accumulation of leptin, it was hypothesized that 5-HT may regulate serum leptin concentrations in a neuron-mediated manner.^{56,57} On the

1 hand, it was reported that fluoxetine, which is an SSRI, can decrease plasma leptin levels in rats.⁵⁸ On the other hand, Hastings et al. found a significantly increased urinary 5-hydroxyindoleacetic acid (the main metabolite of 5-hydroxytryptamine) in hypothalamic tissue of rats injected with leptin,⁵⁶ which suggested that leptin may accelerate the metabolism of 5-HT and lead to a decrease in central 5-HT levels. Therefore, more interest has been focused on the role of leptin as a negative regulator of 5-HT expression. Oury et al. found that leptin may be able to improve 5-HT metabolism by inhibiting the nitric oxide synthesis.⁵⁹ Further, elevated levels of 5-HT can lengthen the IELT and decrease the ejaculatory threshold of the glans penis, thereby improving sexual performance. Rodriguez et al. reported that leptin was able to stimulate NO release through activation of the NO system, which inhibited the contraction of vascular smooth muscle induced by angiotensin II.⁶⁰ Besides, leptin increases sympathetic nerve activity in rodents and humans. Besides, leptin increases sympathetic nerve activity in rodents,⁶¹ which also plays an important role in ejaculatory control. Based on the above findings, we found that leptin may be associated with multiple factors affecting ejaculation, such as 5-HT, sex hormones and NO pathways, suggesting that leptin has potential biomarker value in the diagnosis of PE. A question which may arise is

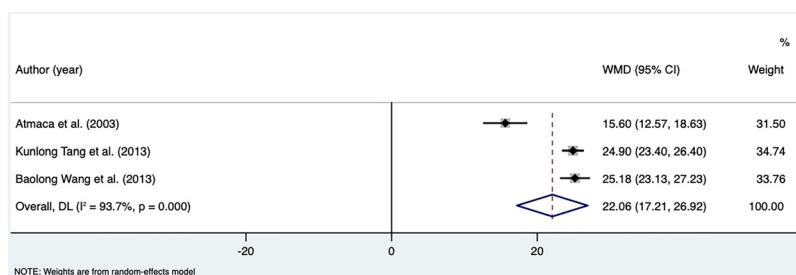


Figure 7. Forest plot for the changes of leptin levels in PE patients before and after SSRIs treatment.

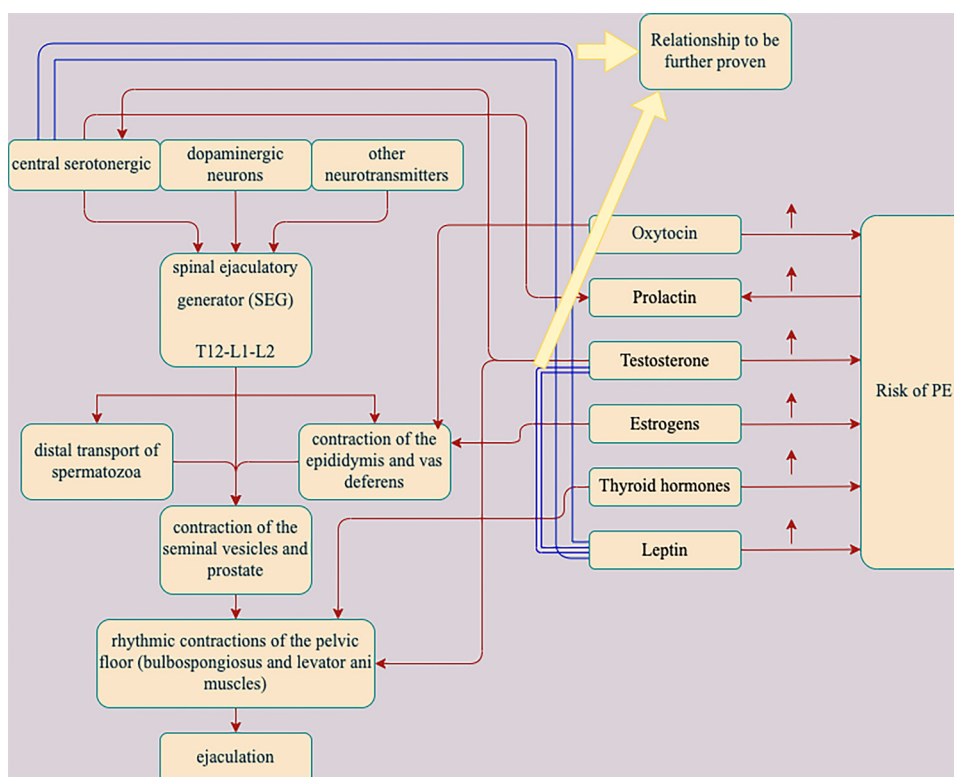


Figure 8. Flowchart of related hormones and ejaculation process.

whether leptin plays a key role in pathophysiology of PE or is just a serum marker?

In our meta-analysis, by combining the pooled data from several selected studies, it was concluded that high serum leptin levels are statistically significant correlated with PE, however, the causal relationship between leptin and PE has remained to be investigated further. The role of leptin in the pathogenesis of PE is unclear. It is likely that higher leptin levels are only a phenotype of PE or a marker of other neuroendocrine changes (like 5-HT),¹⁷ similar to high levels of testosterone in PE patients, and they are not considered causative factors of PE, but rather simple markers of PE.⁴⁷ Another interesting result is that there is a statistically significant decrease in serum leptin levels in PE patients after treatment with SSRIS. However, the exact causal relationship also remains to be further clarified. We acknowledge the fact that serum leptin levels as a single indicator may not be sufficient to predict and diagnose PE, but it is possible to contribute an objective measure to the current diagnostic measures of PE, and it is also worth going into further research to explore its relationship with premature ejaculation in more detail.

Several limitations should be recognized in our meta-analysis. The meta-analysis is a comprehensive report based on the average results of each study we selected, without patient-level data, which causes the loss of some original information of each research in the meta-analysis. On the other hand, the possibility of combining a large number of investigations allows for a much greater statistical power, limiting the problem of casual results

because of small sample size. It is also possible that some of the results noticed here are caused by the effects of unadjusted confounders. Hence, great caution is required in the interpretation of results, which should be confirmed in large-scale observational studies. In addition, a noteworthy limitation is that all the studies we included were from Asia, which may reduce the generalizability of our analysis findings. We will continue to keep an eye on related aspects of research and may conduct original research in related areas in the future to make our conclusions more convincing. Some of the results in our data analysis may also be due to the effects of unadjusted confounders. We performed subgroup analysis, bias detection, and other manipulations to counteract this. Even so, great carefulness is necessary in interpreting the results, and extensive observational studies are still required to further confirm our conclusions.

CONCLUSION

In our meta-analysis, we analyzed data from 5 studies involving serum leptin levels and IIEF-5 scores in patients with premature ejaculation and controls and concluded that serum leptin levels were statistically significantly associated with patients with PE. In addition, we analyzed 3 studies on leptin levels in patients with premature ejaculation before and after treatment, which showed that patients with premature ejaculation also showed a significant decrease in serum leptin levels after 8 weeks of treatment with SSRIs. This suggests that leptin could potentially be a new marker for premature ejaculation.

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STATEMENT OF AUTHORSHIP

Guodong Liu: conception and design; Guodong Liu and Yuyang Zhang: draft and revise the content of the article; Guodong Liu, Yuyang Zhang, Wei Zhang, Xu Wu and Hui Gao: Acquisition of data; Guodong Liu, Yuyang Zhang and Wei Zhang: analysis and interpretation of data; Hui Jiang, Yutian Dai and Xiansheng Zhang: review and editing; Xiansheng Zhang: final approval of the completed article.

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