Sexual function improvement in association with serum leptin level elevation in patients with premature ejaculation following sertraline treatment: a preliminary observation

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Abstract

The objective of our work was to evaluate the effect of sertraline hydrochloride on serum levels of leptin and sexual function in patients with premature ejaculation (PE). A total of 124 patients with a history of PE at least 6 months, aged 20-50 years, were treated with sertraline hydrochloride. One hundred and four age-matched normal males without a history of PE were included control subjects and were untreated. Before and after the 8 week experiment, sexual performance parameters including the intravaginal ejaculation latency time (IELT) and the Chinese premature ejaculation index (CIPE) were collected from both PE patients and control subjects through a questionnaire survey and analyzed. Serum levels of leptin were measured. Correlations of serum leptin with Body Mass Index (BMI) were analyzed. Before sertraline treatment, serum levels of leptin were significantly higher (32.9 vs 8.8μg/L, $p<0.001$) but IELT and CIPE score were significantly lower (54 vs 590, $p<0.001$; 8.7 vs 22.3, $p<0.0001$) in PE patients than control subjects. After 8 weeks of treatment with sertraline, serum levels of leptinl in PE patients were decreased markedly to 8.0 μg/L, which was not significantly different from the levels in control subjects ($p>0.05$); and IELT and CIPE score in PE patients were increased to the values similar to those in control subjects. The sensitivity and specificity values were 87.5% and 96.3% for leptin as a diagnosis target. These observations suggest sertraline as a selective serotonin reuptake inhibitor may offer an effective option for treating premature ejaculation.

KEY WORDS: premature ejaculation, therapeutic target, serum leptin, diagnosis, treatment

INTRODUCTION

Premature ejaculation (PE), first reported in 1887, is one of the most common forms of sexual dysfunction and occurs in approximately 25% - 40% of adult males [1, 2]. To date, there are no objective and accurate diagnosis and effective therapies available for PE. Based on recent findings from both human and animal studies, Waldinger and colleagues have postulated that PE is mainly a neurobiological disorder, which is probably related to changes in serotonergic neurotransmission (5-hydroxytryptamine [5-HT]) in the central nervous system regulated by genetic factors [3]. It is now becoming evident that 5-hydroxytrytamine (5-HT) is a potent inhibitor of ejaculation. A decrease in the content of central 5-HT is a risk factor for PE. Therapeutic benefits of selective serotonin reuptake inhibitors (SSRIs) have been observed in PE patients in clinical settings, confirming a role for 5-HT in the management of PE [4,5]. Leptin is a 16 kDa protein hormone that plays a key role in regulating energy intake and energy expenditure. Since the successful cloning of the leptin gene in 1994, the expression of leptin has been extensively studied. Elevated leptin expression has been observed in obese ob/ob mice [6], and changes in the level of leptin in association with coronary atherosclerosis [7], short sleep duration [8], breast carcinoma [9], hypertension [10] , etc. have been demonstrated. Moreover, it has been suggested that leptin may decrease the content of central 5-HT or inhibit the activity of 5-HT, thereby playing an important role in the development of PE [11-13]. Paroxetine, Sertraline and Fluoxetine are common SSRIs used to treat PE. The efficacy of these SSRIs has been previously evaluated [14-17]. However, little is known regarding

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the effect of these drugs on the expression of leptin. This study aimed to analyze changings in serum levels of leptin in PE patients before and after Sertraline treatment. Given reports of an inadequate ejaculatory control, especially in men with a high BMI [18-20], in the literature, we also attempted to analyze the correlation between BMI and PE.

MATERIALS AND METHODS

Patients

A total of 124 PE patients who were seeking treatment in the urologic surgery clinic of our hospital between May 2011 and May 2012 were recruited. The inclusion criteria were: male at the age of 20-50 years; ejaculation before or shortly after penis penetration into the vagina (duration below 2 min) during a sex intercourse; a history of PE for at least half a year; and no drug treatment in the past 3 months. One hundred and four age-matched subjects with normal ejaculation who were seeking medical treatment for minor respiratory system infection were recruited from the general population in the outpatient clinic as controls. Patients who had a long-term medication history, genitourinary system congenital malformation, neuropathic disease or history of mental illness, erectile dysfunction or long-term alcohol dependence were excluded. The study has been approved by our hospital ethics committee in January 2011 (approval number TMU-01-23). All subjects signed a written informed consent form.

Drug treatment

PE patients were treated with sertraline (Pfizer, USA) for 8 weeks (dose of 50 mg/time, 1 time/day) while control subjects were untreated. All subjects were asked to have regular sexual activities during the study period.

Clinical assessment

Before and after the 8-week experiment, all subjects were asked to complete a PE symptom questionnaire. Information on the intravaginal ejaculation latency time (IELT) and the Chinese sexual function index for premature ejaculation (CIPE); difficulty in prolonging sexual intercourse, sexual satisfaction, partner's sexual satisfaction, level of anxiety in the sexual intercourse collected. A blood sample (6 ml from elbow vein blood) was collected from each of the subjects. Serum was prepared by centrifuging the blood at 1000 g for 10 min and stored at -20°C. Serum levels of leptin were measured by an enzyme linked immunosorbent assay (ELISA) (Cusabio, California, USA) as instructed by the manufacturer. A scatter diagram was plotted to show the distribution of the serum leptin level data; a receiver operator characteristic (ROC) curve was drawn to evaluate the sensitivity and specificity of serum leptin as a PE diagnostic index.

Statistical analysis

SPSS 17.0 software (Chicago, IL, USA) was used. Normal distribution data were expressed as mean ± standard deviations (SD) and analyzed by Student's t test or chi-square test. Relationships of serum levels of leptin with IELT and CIPE score were assessed by Pearson correlation analysis. Differences were considered significant when $p<0.05$.

RESULTS

Differences between PE patients and control subjects

Of the 124 PE patients, 8 developed adverse reactions to sertraline (erectile dysfunction in 4 cases, nausea in 2 cases and urinary retention in 2 cases) and 8 failed to complete the follow-up and dropped out of the study. As a result, 108 PE pa-

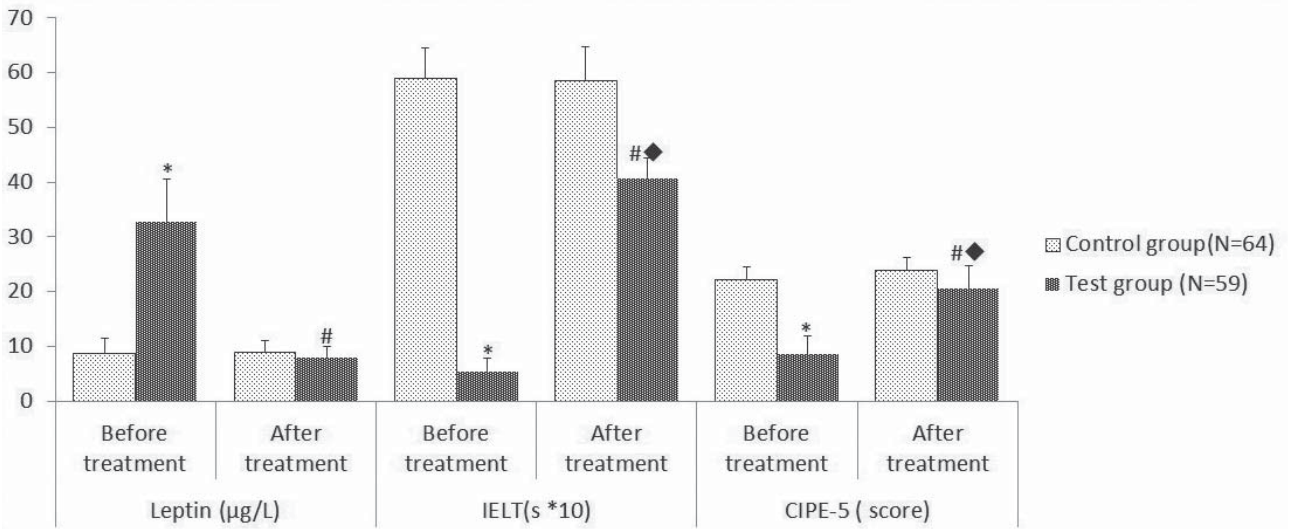

FIGURE 1. Comparison of leptin level, IELT and CIPE score between patients and controls before and after treatment. *, $p<0.05$ vs control before treatment; #, $p<0.05$ vs test group before treatment; ◆, $p<0.05$ vs control group after treatment.

TABLE 1. Basic demographics, sexual function parameters and serum leptin concentrations in PE patients and control subjects prior to the experiment.

	PE patients	Control subjects	*p* value
Age (yr)	30.27 ± 6.48	32.92 ± 7.39	0.071
BMI (kg/m^2)	23.99 ± 3.26	24.20 ± 4.77	0.840
IELT (seconds)	54 ± 25*	590 ± 54	0.000
CIPE (score)	8.7 ± 3.1*	22.3 ± 2.3	0.000
Leptin (μg/L)	32.9 ± 7.7*	8.8 ± 2.6	0.000

TABLE 1. Improvement in sexual performance and serum levels of leptin in PE patients after drug treatment.

	Patient	Control	*p* value
IELT (second)	407 ± 36	585 ± 61	>0.05
CIPE (score)	20.6 ± 4.2	23.9 ± 2.4	>0.05
Leptin (μg/L)	8.0 ± 1.9	8.7 ± 2.2	>0.05

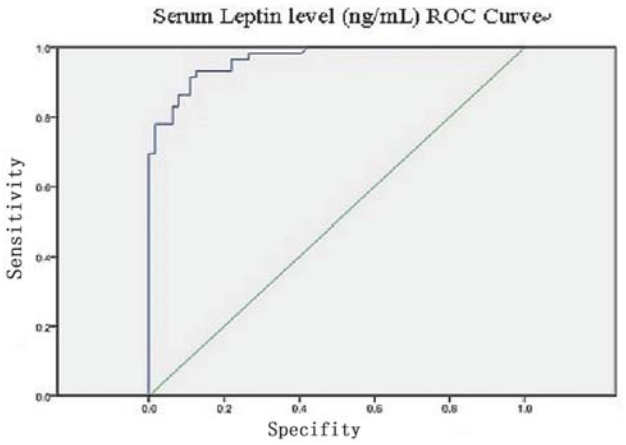

FIGURE 3. ROC curve for serum leptin value as a biomarker of Premature ejaculation

tients and 104 control subjects were included in the final analysis. Presented in Table 1 are their basic demographics, sexual performance parameters and serum leptin levels before sertraline treatment. There were no significant differences in the average age and mean BMI between PE patients and control subjects. The IELT, CIPE and serum leptin levels were significantly different in PE patients before sertraline treatment.

Effects of sertraline treatment

After sertraline treatment, IELT and CIPE in PE patients increased significantly to 407 ± 36 second and 20.6 ± 4.2, while the level of serum leptin decreased markedly to 8.0 ±1.9 μg/L (Figure 1). All these values were improved so significantly (p<0.05) that they were not significantly different from the corresponding values in control subjects (Table 2).

Correlation between BMI, serum levels of leptin and sexual function in PE patients

There was no noticeable correlation between the level of serum leptin and BMI in PE patients before treatment (Figure 2a) but there was a positive relationship between the level of serum leptin and BMI in control subjects (correlation=0.71, p =0.000) (Figure 2b); the higher the BMI value, the higher the level of serum leptin was. After treatment, there was a positive relationship between the level of serum leptin and BMI in PE patients (correlation=0.456, p=0.000) (Figure 2c). ROC curve According to the results of leptin in the test and control groups, the ROC curve was drawn to evaluate the efficacy of serum leptin as a PE diagnostic indicator. As a diagnostic value, the greater the areas under the ROC curve (AUC-ROC), the higher it is. The AUC-ROC of leptin was 0.966; there was a statistically significant diagnostic value compared with the AUC-ROC value of 0.5 (p<0.01). Based on the sensitivity and specificity of leptin ROC curve, the cutoff value corresponded to the maximum Youden index is15.2 μg/L, the sensitivity is 87.5%, and the specificity is 96.3% with 95% CI of 0.84 to 0.95 (p<0.01) (Figure 3).

DISCUSSION

PE is diagnosed mainly by patient's medical and sexual history. Measurements of urine parameters, and sex and other relevant endocrine hormones as well as vaginal B-ultrasonic exam,

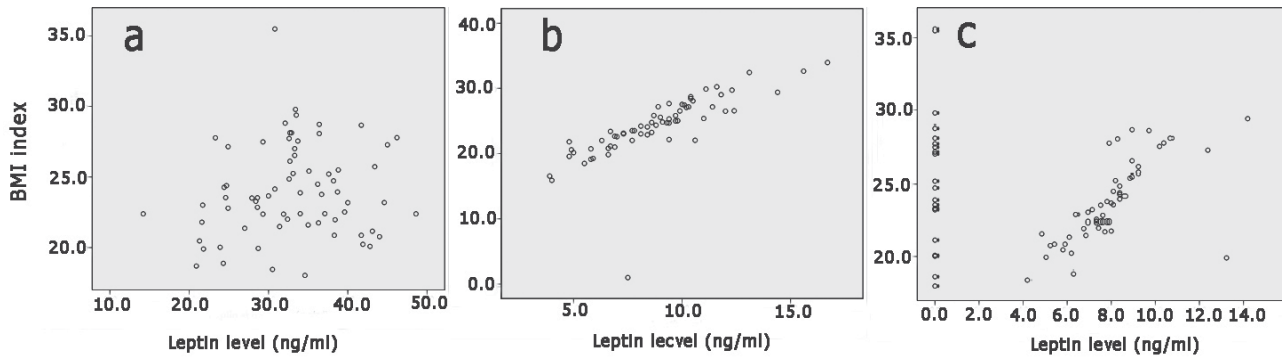

FIGURE 2. Correlation analysis of leptin level and index of BMI between patients with PE and controls. a) No correlation in the patients before treatment; b) A positive relationship in the controls before treatment (correlation=0.71, p =0.000); c) A positive relationship in the patients after treatment (correlation=0.456, p=0.000).

prostate exam and nervous system exam were all non-specific and not recommended conventionally. It is urgent to develop novel effective diagnostic tests and therapeutic strategies. Compiling experimental evidence have showed 5-HT is an effective inhibitor to PE. When 5-HT content is decreased, PE patients tend to exhibit some degree of anxiety during a sexual intercourse. Suggestively, 5-HT may not only affect sexual expression but also induce dysfunction of the relevant nerve innervation. A reduced intracerebral serotonin level in monoaminergic pathways may be related to depression [5]. However, Waldinger [21, 22] suggests that primary PE may be induced by neurobiological and genetic factors and that medications targeting these factors may be effective to treat PE patients. The discovery of selective 5-HT reuptake inhibitors has prompted extensive investigations into the therapeutic value of these inhibitors in PE patients. A previous study [23] has shown that SSRIs may influence synaptic transmission in the brain, leading to a high level of 5-HT and activation of 5-HT receptor on postsynaptic membrane by inhibiting 5-HT reuptake on the membrane, thus delaying ejaculation by elevating the ejaculation threshold. Sertraline used in this study is an antidepressant of the SSRI class. This drug may improve sexual performance through increasing 5-HT content in the blood in patients with PE. Leptin is an adipokine that was originally identified as a key molecule in the regulation of food intake and body weight [24]. Leptin is found to have a biologically active free form and presumably an inactive form in the circulation and obese individuals typically produce higher levels of leptin than leaner individuals [25, 26]. In addition, recent studies have indicated an aberrant expression of leptin in many disease conditions [27-29]. Moreover, this protein hormone may also play a role in regulating sexual function. Several previous studies have demonstrated that serum levels of leptin are significantly higher in PE patients than healthy controls [13, 32]. Our observations on serum levels of leptin in PE patients and control subjects were consistent with results from these studies. Recent studies have showed that leptin and 5-HT may regulate each other's expression. Some researchers have found that decreasing of 5-HT in rat hypothalamus tissue may lead to an accumulation of leptin, speculating that 5-HT may modulate the serum leptin concentration through a way mediated by neurons [11, 30, 31]. Hastings et al. [11] have found that 5-hydroxyindole acetic acid (the main metabolite of serotonin) in urine is significantly increased in the rat hypothalamus tissues injected with leptin, indicating that leptin may speed up metabolism of 5-HT leading to a decrease in the central 5-HT content. Accordingly, more attention has been paid to the effect of leptin as a negative regulator of 5-HT expression. Oury et al. [12] has found that leptin may promote metabolism of 5-HT by inhibiting the synthesis of nitrous oxide. A high concentration of 5-HT may extend the IELT and reduce the ejaculation threshold of glans penis, thereby improving sexual performance.

CONCLUSION

In summary, we observed that serum levels of leptin in patients with PE were significantly higher than that in the control group prior to treatment and that serum levels of leptin in the patients were correlated with the degree of severity of the disease. These observations suggest a biomarker value for leptin in the diagnosis of PE.

DECLARATION OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Hellstrom WJ. Update on treatments for premature ejaculation. Int J Clin Pract 2011;65(1):16-26.
[2] McMahon CG, Lee G, Park JK, Adaikan PG. Premature ejaculation and erectile dysfunction prevalence and attitudes in the Asia-Pacific region. J Sex Med 2012;9(2):454-465.
[3] Waldinger MD. The neurobiological approach to premature ejaculation. J Urol 2002; 168(6):2359-2367
[4] Giuliano F. 5-Hydroxytryptamine in premature ejaculation: opportunities for therapeutic intervention. Trends Neurosci. 2007;30(2):79-84.
[5] Savitz J, Lucki I, Drevets WC. 5-HT(1A) receptor function in major depressive disorder. Prog Neurobiol 2009; 88(1):17-31.
[6] Johnson MS, Huang TT, Figueroa-Colon R, Dwyer JH, Goran MI. Influence of leptin on changes in body fat during growth in African American and white children. Obes Res. 2001; 9(10):593-598.
[7] Reilly MP, Iqbal N, Schutta M, Wolfe ML, Scally M, Localio AR, et al. Plasma leptin levels are associated with coronary atherosclerosis in type 2 diabetes. J Clin Endocrinol Metab. 2004;89(8):3872-3878
[8] Chaput JP, Despres JP, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: Results from the Quebec family study. Obesity (Silver Spring). 2007;15(1):253-261.
[9] Snoussi K, Strosberg AD, Bouaouina N, Ben Ahmed S, Helal AN, Chouchane L. Leptin and leptin receptor polymorphisms are associated with increased risk and poor prognosis of breast carcinoma. BMC cancer. 2006;6:38.
[10] Almeida-Pititto B, Gimeno SG, Freire RD, Ribeiro-Filho FF, Ferreira SR; Japanese-Brazilian Diabetes Study Group. Leptin is not associated independently with hypertension in Japanese-Brazilian women. Braz J Med Biol Res. 2006;39(1):99-105
[11] Hastings JA, Wiesner G, Lambert G, Morris MJ, Head G, Esler M. Influence of leptin on neurotransmitter overflow from the rat brain in vitro. Regul Pept. 2002;103(2-3):67-74.
[12] Oury F, Karsenty G. Towards a serotonin-dependent leptin roadmap in the brain. Trends in endocrinology and metabolism: TEM. 2011;22(9):382-387.
[13] Nikoobakht MR, Tajik P, Karami AA, Moradi K, Mortazavi A, Kosari F. Premature ejaculation and serum leptin level: a diagnostic case-control study. J Sex Med 2008;5(12):2942-2946
[14] Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorders--III. Tolerability, safety and pharmacoeconomics. J Psychopharmacol. 1998;12(3 Suppl B):S55-87.

[15] Ferguson JM. SSRI Antidepressant Medications: Adverse Effects and Tolerability. Prim Care Companion J Clin Psychiatry 2001;3(1):22-27.
[16] Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373(9665):746-758.
[17] Aberg-Wistedt A, Agren H, Ekselius L, Bengtsson F, Akerblad AC. Sertraline versus paroxetine in major depression: clinical outcome after six months of continuous therapy. J Clin Psychopharmacol 2000; 20(6):645-652.
[18] Aversa A, Francomano D, Bruzziches R, Natali M, Guerra A, Latini M, et al. A pilot study to evaluate the effects of vardenafil on sexual distress in men with obesity. Int J Impot Res 2012;24(3):122-125.
[19] Andersen I, Heitmann BL, Wagner G. Obesity and sexual dysfunction in younger Danish men. J Sex Med. 2008;5(9):2053-2060
[20] Christensen BS, Gronbaek M, Pedersen BV, Graugaard C, Frisch M. Associations of unhealthy lifestyle factors with sexual inactivity and sexual dysfunctions in Denmark. J Sex Med. 2011;8(7):1903-1916.
[21] Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. Behav Brain Res 1998; 92(2):111-118.
[22] Waldinger MD. Premature ejaculation: different pathophysiologies and etiologies determine its treatment. J Sex Marital Ther. 2008; 34(1):1-13.
[23] Giuliano F, Clément P. Serotonin and premature ejaculation: from physiology to patient management. Eur Urol. 2006; 50(3):454-466.
[24] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372(6505):425-432.
[25] Kissileff HR, Thornton JC, Torres MI, Pavlovich K, Mayer LS, Kalari V, et al. Leptin reverses declines in satiation in weight-reduced obese humans. Am J Clin Nutr 2012; 95(2):309-317.
[26] Anagnostis P, Selalmatzidou D, Sapranidis M, Panagiotou A, Polyzos SA, Slavakis A, et al. Comparative effects of sibutramine and orlistat on weight loss, glucose metabolism and leptin levels in non-diabetic obese patients: A prospective study. Indian J Endocrinol Metab. 2012;16(1):146-147.
[27] Shankar A, Syamala S, Xiao J, Muntner P. Relationship between plasma leptin level and chronic kidney disease. Int J Nephrol 2012;2012:269532.
[28] Beccano-Kelly D, Harvey J. Leptin: a novel therapeutic target in Alzheimer's disease? Int J Alzheimers Dis. 2012;2012:594137.
[29] Monreal M. The tumor necrosis factor system and leptin in coeliac disease. Med Clin (Barc) 2012;139 (Suppl 2):1-3.
[30] Fernández-Galaz MC, Fernández-Agulló T, Carrascosa JM, Ros M, Garcia-Segura LM. Leptin accumulation in hypothalamic and dorsal raphe neurons is inversely correlated with brain serotonin content. Brain Res 2010;1329:194-202.
[31] Desai M, Gayle D, Han G, Ross MG. Programmed hyperphagia due to reduced anorexigenic mechanisms in intrauterine growth-restricted offspring. Reprod Sci. 2007;14(4):329-337.