Serum leptin levels in patients with premature ejaculation before and after citalopram treatment

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Accepted for publication 3 November 2002

OBJECTIVE

To evaluate serum leptin levels (an adipocyte hormone involved in the suppression of appetite) in patients with premature ejaculation before and after treatment with citalopram, a selective serotonin reuptake inhibitor, with the hypothesis that leptin levels might become normal during this treatment.

PATIENTS AND METHODS

The inhibitory effect of serotonin on libido, ejaculation and orgasm is well documented. Although there is no direct evidence of an association involving brain pathways which are related to sexual behaviour, there is an interaction between leptinergic and serotonergic systems. In a previous study serum leptin levels were high in patients with premature ejaculation. The present study comprised 30 patients with premature ejaculation according to the Diagnostic and Statistical Manual of Mental Disorders Third Revised Version. Fifteen patients (group I) were randomly assigned to 8 weeks of citalopram treatment and the remainder (15, group II) received no therapy. The patients were asked to determine the average intravaginal ejaculation latency time, and their fasting serum leptin levels were measured at baseline and after 8 weeks.

RESULTS

There was no significant difference in the mean intravaginal ejaculation latency time between the groups at baseline; it increased after 8 weeks of treatment with citalopram in group I, to a mean (SD) of 209 (72.1) s, but not in group II. No difference was detected in leptin levels between the groups at baseline, but at 8 weeks they were lower in group I.

CONCLUSION

As hypothesized, leptin levels decreased in patients with premature ejaculation after treatment with citalopram, and this decrease seemed to be linked to the therapeutic effect. Further experimental studies are needed.

KEYWORDS

leptin, premature ejaculation, serotonin, citalopram

INTRODUCTION

Premature ejaculation has been defined as uncontrolled ejaculation, the essential feature of which is recurrent or persistent orgasm with minimal sexual stimulation beforehand, on or after penetration and before the person desires it. Most men with premature ejaculation can delay ejaculation and orgasm during self-masturbation for considerably longer than during coitus [1].

The inhibitory effect of serotonin on libido, ejaculation and orgasm is well documented, and has been attributed to a serotonin-induced decrease in dopamine (a neurotransmitter enhancing sexual function) level in the CNS [2,3]. Methylene-dioxy-metamphetamine (better known as ecstasy) induces serotonin and dopamine release with a central action, and causes an increase in libido and sexual satisfaction by dopamine release, while causing delay and prominent inhibition of ejaculation and orgasm by serotonin activation [4]. Selective serotonin reuptake inhibitors (SSRIs) are reported to be effective for treating premature ejaculation [5,6]. The presumed mechanism of these drugs is the enhancement of net serotonergic transmission by blocking the presynaptic 5-hydroxytryptamine uptake site [7]. Leptin is a fat-cell-derived hormone which signals the hypothalamus about food intake, the regulation of weight and sexual behaviour, and so it is thought to lead to suppression of appetite, weight loss and acceleration of sexual maturation, and to stimulate energy expenditure [8,9]. Zhang *et al.* [10] reported that it is a product of the *ob* gene. The association between leptin and various psychiatric disorders has been noted [11–14]; moreover, there is an interaction between the leptinergic and serotonergic systems in the CNS [15] and leptin has no significant effect on hypothalamic noradrenaline overflow, while leptin perfusion induces a significant increase in 5-hydroxy indole acetic acid overflow from the hypothalamus [15,16]. In our previous study [12], there were significantly high serum leptin levels in patients with premature ejaculation, after adjusting for body mass index or age. These associations prompted an assessment of whether there would be a change in serum leptin levels in patients with premature ejaculation before and after treatment with citalopram, an SSRI, and we hypothesized that leptin levels might become normal during this treatment.

PATIENTS AND METHODS

The study comprised 30 married men (aged 23–42 years) who had presented to our institution, and had been diagnosed with premature ejaculation according to the Diagnostic and Statistical Manual of Mental Disorders Third Revised Version (DSM-III-R) [17] and met the study admission criteria. The patients were randomly assigned to two groups on a double-blind basis, determined by a computer-generated schedule. Fifteen patients (group I) received citalopram for 8 weeks while the remainder received no therapy (behavioural or pharmacological).

Each patient was evaluated diagnostically in detail by one trained psychiatrist using the Structured Clinical Interview for DSM-III-R outpatient form [18]. Patients with any kind of comorbid psychiatric disorder were excluded. To be able to exclude organic sexual dysfunctions, fasting glucose level, urine analysis, complete blood count, sex hormones and prolactin levels were measured. All

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Mean (SD) variable	Group I	Group II
Age, years		
patients	31.5 (7.9)	27.8 (5.3)
partners	30.3 (6.8)	28.6 (4.9)
Duration of condition, months	2.3 (15.6)	79.8 (13.8)
BMI, kg/m^2	23.7 (1.9)	23.3 (2.3)
IELT, s		
at baseline	38.5 (14.7)	36.2 (16.1)
at 8 weeks	247.9 (117.8)	41.1 (13.3)*
Final dose of citalopram, mg	30.7 (9.3)	–
Leptin, ng/mL		
baseline	23.9 (5.3)	24.2 (3.8)
week 8	8.3 (2.8)*	24.9 (3.5)

TABLE 1
The characteristics and other variables assessed before and after treatment with citalopram

*P < 0.001.

patients were free of all medication for at least the previous 2 weeks. Patients were excluded if: they had erectile dysfunction and inhibited male orgasm, a severe physical illness, a history of alcohol and substance abuse or dependence, a previous history of lipid-lowering treatment and any endocrinological state. All participants were heterosexual.

All patients were carefully assessed to exclude autoimmune, pulmonary, infectious diseases and neoplasms. Their body mass index (BMI) was calculated. They were asked to determine the average intravaginal ejaculation latency time (IELT) for three consecutive episodes of coitus, verified by both patients and their wives, using a chronometer. The IELT was defined as the duration between vaginal intromission and ejaculation. The patients and their wives were encouraged to have coitus at least twice per week. Patients in group I initially received 20 mg/day citalopram for 1 week; this was titrated up to 60 mg/day according to the patient's tolerability and clinical response. In addition, they were asked to report adverse effects using an instrument designed by the authors which included all side-effects reported that were related to antidepressant use. Thus, side-effects were recorded as 'present' and 'absent'. After describing the study to the patients, written informed consent was obtained from each and ethical permission obtained from the local ethics committee of Firat University School of Medicine.

To determine the serum levels of leptin, all the patients fasted overnight; venous blood samples were drawn from an antecubital vein at 08.00 hours and leptin levels measured using a radioimmunoassay kit (rat leptin kit, Linco Corp., St Charles, MO, USA) in a gamma counter (LKB Wallac 1261, Wallac Corp., Turku, Finland). Normal values are < 10 for males and < 20 ng/mL for females, with a BMI of < 25 kg/m^2. Serum leptin levels were assayed at baseline and after treatment with citalopram for 8 weeks.

The statistical analysis used independent-sample and paired *t*-tests, analysis of covariance (ANCOVA) and Pearson's method of correlation, with differences considered significant at $P < 0.05$ for all tests.

RESULTS

The characteristics of the two groups are shown in Table 1, with the results of treatment. The mean IELT increased significantly after treatment with citalopram. No patient had a significant weight change on citalopram; while one lost 0.6 kg and one 0.4 kg, three gained weight of 0.8, 0.6 and 0.5 kg, respectively.

At baseline, the leptin levels were high in nine patients in group I and in eight in group II, when compared with normal leptin levels adjusted for BMI and age. There was no significant difference in serum leptin levels between the groups at baseline, adjusted for BMI (ANCOVA). At 8 weeks the mean leptin level was significantly lower than baseline (ANCOVA with BMI as the covariate, $P < 0.05$, adjusted for BMI) in group I ($P < 0.001$), but not in group II.

There was a positive correlation between leptin levels and BMI in both groups at baseline ($r = 0.62$ and 0.56, $P < 0.05$ for groups I and II, respectively) and at 8 weeks ($r = 0.58$ and 0.54, both $P < 0.05$). Correlation analysis between leptin levels and age showed no statistical significance in both groups (respectively at baseline and 8 weeks, $r = 0.08$ and 0.06 for group I, and 0.17 and 0.12 for group II). There was also a positive correlation between leptin levels and the duration of the condition, at baseline, in both groups ($r = 0.61$ and 0.56 for groups I and II, respectively).

Citalopram was well-tolerated; there were 14 reports of adverse effects from eight patients, the most frequent being gastrointestinal complaints (four) and insomnia (three). No patient withdrew from the study because of adverse events.

DISCUSSION

The major findings of the present study are that citalopram treatment considerably increased the IELT and that there was a positive correlation between leptin levels and the duration of the condition. SSRIs have been suggested as an effective treatment for premature ejaculation [5,6]. In the present study, citalopram, the most selective SSRI [19], produced considerable improvements in patients with premature ejaculation, even though the study had methodological limits, e.g. relatively few patients. The effect of serotonin on premature ejaculation and other sexual dysfunction was hypothesized from the observations that imipramine was associated with more significant sexual dysfunction than desipramine, and the inhibition of antidepressant-induced orgasm could be reversed by a nonselective serotonin antagonist, cyproheptadine [20,21]. Fluoxetine, an SSRI, has been reported to reduce the plasma leptin levels in rats [22], which was supported by the present study using a different SSRI (citalopram); leptin administration also stimulated serotonin turnover [23]. In contrast, in another study which examined whether the co-administration of fluvoxamine (an SSRI) and clozapine (an atypical antipsychotic) influenced immunomodulation by clozapine and some of its side-effects, the two together enhanced the clozapine-induced increase in leptin plasma levels with no significant effect on clozapine-induced weight gain [24]. Hastings *et al.* [16] investigated the interactions between leptinergic and neurotransmitter systems of the rat brain, reporting that leptin had no significant effect on hypothalamic noradrenaline overflow, while leptin perfusion induced a significant increase in 5-hydroxy indole acetic acid overflow from the hypothalamus. In the present study there was a significant correlation between leptin levels and the duration of illness or the IELT; this suggest that an increased severity of illness affects leptin levels, and that as the illness becomes

chronic the association becomes more marked.

There are some limitations in the present study; first, the lack of placebo control and short duration of treatment, and second, there were relatively few patients, who might not be representative of those with premature ejaculation. Moreover, we were unable to assess economic status, other psychosocial factors and dietary differences which might affect serum leptin levels. In summary, the present results provide further evidence that leptin may be associated with premature ejaculation, although there were too few patients to permit clear conclusions. Leptin levels in patients with premature ejaculation decreased after treatment with citalopram, as hypothesized, and this decrease seemed to be linked to the therapeutic effect. However, more comprehensive and detailed studies of leptin and indices of serotonin are needed to determine the exact role of leptin in premature ejaculation. Future studies with more patients, a placebo control and a substance known to reduce leptin levels, but which would not normally be expected to influence ejaculation, should be used.

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Abbreviations: **SSRI**, selective serotonin reuptake inhibitor; **DSM-III-R**, Diagnostic and Statistical Manual of Mental Disorders Third Revised Version; **BMI**, body mass index; **IELT**, intravaginal ejaculation latency time; **ANCOVA**, analysis of covariance.