Evaluation of leptin levels among fibromyalgia patients before and after three months of treatment, in comparison with healthy controls

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BACKGROUND: Leptin, an adipocyte-produced cytokine, interacts with various hormones, including those of the hypothalamic-pituitary-adrenal axis. Fibromyalgia is a syndrome characterized by widespread pain accompanied by tenderness. The pathogenesis involves a disturbance in pain processing and transmission by the central nervous system, leading to a general increase in pain perception.

OBJECTIVES: To analyze potential changes in leptin levels among female fibromyalgia patients compared with healthy controls, and to evaluate the changes in leptin levels during treatment.

METHODS: Sixteen female fibromyalgia patients were recruited. Patients underwent clinical evaluation, physical examination, including manual dolorimetry, and were evaluated regarding quality of life, pain, fatigue, anxiety and depression. Plasma leptin levels were determined by ELISA. Patients were offered standard treatment for fibromyalgia. Clinical evaluation and leptin determination were repeated after three months.

RESULTS: No significant difference was observed between leptin levels among fibromyalgia patients and controls; no significant correlation was observed between leptin levels and clinical parameters reflecting fibromyalgia severity; and no significant change was observed in leptin levels over three months of treatment. These results did not change after adjustment of leptin levels for body mass index values.

CONCLUSIONS: The results of the present study do not support the existence of a significant relationship between leptin and fibromyalgia pathogenesis. Increasing the sample size or examining the interaction between leptin and additional hormones/mediators of metabolism and body weight control may yet uncover significant information in this field.

Key Words: Chronic pain; Fibromyalgia; Leptin

Leptin levels are higher in women compared with men (7), and secretion is characterized by a diurnal variation, with maximal levels observed during the night (8). In animal models, leptin has been shown to inhibit the response of the HPA axis to stress by inhibiting the secretion of cortisol-releasing hormone (9). A complex interaction between leptin and the HPA is demonstrated by the finding of decreased leptin levels together with HPA activation during surgical stress (10). Moreover, while leptin inhibits the HPA, it is itself stimulated by glucocorticoids, endotoxins and cytokines (11). Depression and schizophrenia have both been associated with decreased leptin levels (12), while treatment with antipsychotic medications causes both weight gain and an increase in leptin levels (13). In addition, multiple lines of evidence point toward a role in leptin in the immune system. In rat and mouse models, leptin has been shown to reduce the threshold for pain (14). Leptin has also been shown to increase levels of interleukin-1, a cytokine known to cause hyperalgesia (15). Leptin...
obtained for determination of leptin levels. Control individuals did not undergo a repeat examination.

In view of this background, and particularly in light of the roles and interactions between leptin and the immune system, the HPA system as well as the effect on pain threshold, the present study aimed to evaluate the possibility of an alteration in levels of leptin patients suffering from fibromyalgia, a prototypical disorder of central pain processing.

METHODS

Sixteen female fibromyalgia patients were recruited from the fibromyalgia clinic at the Tel Aviv Sourasky Medical Center Rheumatology Institute (Tel Aviv, Israel). The patients underwent clinical evaluation that included manual dolorimetry, tender point evaluation and count. Weight and height were documented, and body mass index (BMI) was calculated. Demographic details and medical history were documented. Fulfillment of 1990 American College of Rheumatology classification criteria of fibromyalgia was documented (18). Written informed consent was obtained from all patients and the study protocol was approved by the institutional Helsinki committee.

Plasma samples were obtained on recruitment for leptin determination. Twenty-one healthy female individuals were recruited as the control group. Patients receiving long-term medical treatment for fibromyalgia (eg, SSRIs) were excluded, as well as patients treated during the preceding four weeks. The use of short-term analgesics such as acetaminophen was permitted.

Quality of life evaluation

The following questionnaires were used for evaluation of quality of life and impact of fibromyalgia on the patients:

- The Short-Form-36 Health Survey (SF-36), a 36-item questionnaire assessing various aspects of quality of life, including physical and mental components. This tool has been previously tested and validated for measuring quality of life in patients with fibromyalgia (19).
- Based on the response to these questions, the Mental Component Summary (MCS) and the Physical Component Summary (PCS) were calculated (20).
- The Fibromyalgia Impact Questionnaire (FIQ), which expresses the effect the fibromyalgia syndrome (FMS) has on the patient's quality of life, based on the reported severity of symptoms (reported on a visual analogue scale); parameters such as fatigue, depression, anxiety and pain are included. In the current study, a validated translation of the Hebrew version of the FIQ was used (21).
- The depression and anxiety questionnaires taken from the Arthritis Impact Measurement Scale (AIMS) scale were also used (22).

On recruitment, all patients received general explanations on the nature of their medical problem and were instructed about the value of physical activity in fibromyalgia. The use of medications for the treatment of fibromyalgia such as tricyclic compounds or SSRIs was left to the discretion of the attending rheumatologist on clinical grounds.

Three months after recruitment, patients were invited for a second examination. Basic demographic data regarding patients and controls are summarized in Table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean ± SD</th>
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<tbody>
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<td>Age, years</td>
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<tr>
<td>Patients</td>
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<td>50.44±9.61</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
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<td></td>
</tr>
<tr>
<td>Control</td>
<td>21</td>
<td>26.55±5.66</td>
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<tr>
<td>Patients</td>
<td>16</td>
<td>25.55±4.55</td>
</tr>
</tbody>
</table>

To take into consideration the effect of BMI on levels of leptin, a calculation was performed based on one-way ANOVA with covariance. No significant change was observed between the groups after adjustment for BMI.

To evaluate the effect of medical treatment on leptin levels, results were analyzed after dividing the patients into subgroups of those treated and those not treated with medications. No significant change was observed between the treated and untreated groups, including after BMI adjustment.

Statistical analysis

Comparison of the two study groups (fibromyalgia patients and controls) regarding clinical and demographic data at outcome was performed with the use of the t test for independent samples. Comparison between the patients regarding leptin levels before and after three months of treatment was performed using ANOVA after adjustment for BMI.

RESULTS

Sixteen patients fulfilling American College of Rheumatology criteria for classification of fibromyalgia were recruited, as were 21 healthy controls. All individuals recruited were females. Thirteen patients returned for a second examination. Basic demographic data regarding the patients and controls are summarized in Table 1.

Determination of leptin levels

Samples of venous blood were drawn between 08:00 and 09:00 into test tubes containing EDTA. Samples underwent centrifugation and plasma was kept at −20°C until processing. Levels of leptin were determined by the use of a commercial ELISA kit (Linco Research Incorporation, USA). The test's sensitivity was 0.5 ng/mL and the interassay coefficient of variation was in the range of 3% to 6%.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Leptin 0*</th>
<th>n</th>
<th>Leptin 2†</th>
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<td>Control</td>
<td>21</td>
<td>15.96±8.90</td>
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<td>16</td>
<td>15.74±7.30</td>
<td>13</td>
<td>18.10±7.84</td>
</tr>
</tbody>
</table>

*Leptin 0: Leptin levels (mean ± SD) at recruitment (ng/mL); †Leptin 2: Leptin levels (mean ± SD) after three months of treatment (ng/mL)
parameters was evaluated. The results showed no statistically significant correlation between these parameters.

Notably, no significant improvement was observed in the clinical parameters of fibromyalgia patients evaluated, based on FIQ and SF-36 parameters (MCS and PCS).

**DISCUSSION**

The present study attempted to evaluate the relationship between fibromyalgia and serum levels of leptin. The results do not support the existence of a significant difference in serum levels of leptin between fibromyalgia patients and healthy controls. In addition, no significant change was observed in leptin levels before and after three months of standard treatment for fibromyalgia. As described in the introduction, leptin has a significant role in the regulation of the stress response, including the response of the HPA axis to stress (23,24) as well as in pain regulation (25), while a counterbalance has been described between levels of leptin and levels of cortisol in fibromyalgia (26). In view of this background, an association between serum leptin levels and fibromyalgia per se or fibromyalgia severity appeared plausible.

The lack of evidence of such a relationship in the current study may be attributed to several factors. The small size of the study sample may have limited our ability to identify a small effect. The heterogeneity in the treatment received, as well as the short period of follow-up, may similarly have limited our capacity to identify the effect of treatment on the leptin levels. Also, the lack of a significant clinical effect in the present study is an obvious limitation. This finding may reflect the difficulty in achieving significant improvement in FMS patients, as well as the inconsistent implementation of recommended and evidence-based treatment modalities. The lack of a change in leptin levels during the period of the study is also not surprising, considering the lack of a significant difference at baseline between patients and controls.

Nonetheless, we consider the comparison between fibromyalgia patients and controls to be the more significant finding of our study, which was not powered to evaluate a response to treatment. It is also noteworthy that, in the present study, no intervention was conducted regarding the treatment strategy of the patients, who were managed by the attending physicians according to clinical discretion. The fact that most patients were treated with SSRIIs (rather than with more evidence-based treatments such as pregabalin and SNRIs) may point to insufficient awareness regarding optimal management of the FMS. In addition, it may reflect difficulties with insurance coverage because no medications have, to date, been introduced into national health insurance coverage in Israel for the fibromyalgia indication.

The possibility also exists that additional factors apart from leptin, which participate in the regulation of the metabolic rate, may play a more complex role in the pathogenesis of fibromyalgia. Thus, mediators such as ghrelin and neuropeptide-Y (27) have been shown to play a role in the pathogenesis of fibromyalgia and in the body’s response to stress (28). Thus, it may be that the interaction among several metabolic mediators is more significant than the level of one particular player, as assessed in the present study.

Regarding the apparent lack of effect of treatment on leptin levels in the present study, it must be pointed out that various studies have previously demonstrated an effect of medications such as SSRIIs (28,30), often prescribed for fibromyalgia patients, on leptin levels as well as an association between leptin levels and depression (31). In the present study, five of 16 patients were treated with an SSRI or an SNRI. No significant change was discerned regarding the AIMS and MCS parameters, expressing levels of anxiety and depression. Concurrently, no change was observed in leptin levels. Thus, it is possible that the observed lack of effect on leptin levels is the result of the relatively small sample size and short duration of treatment that precluded a more profound effect of SSRI/SNRI treatment.

Our results contrast with those previously reported by Fietta and Fietta (26), as noted above, who reported in a small study the finding of a counterbalance between leptin and cortisol in FMS patients. The authors of that study raised the possibility that leptin may play a role in maintaining a state of hypervigorilence in FMS, similar to the post-traumatic state. Notably, all patients in their study were reported to be untreated and, thus, it is possible that the effects of treatment may have masked a difference in our study.

Leptin levels are influenced by BMI; in the present study, as in the study by Fietta and Fietta (26), nonobese patients were recruited, patients and controls were matched for BMI and comparisons of leptin levels were adjusted for BMI. Another possible confounder relates to the effect of the menstrual cycle on leptin levels. Leptin levels are known to peak during the luteal phase compared with the follicular phase (32). Thus, comparing patients who were synchronized regarding the menstrual cycle, as well as excluding menopausal patients, may have improved accuracy and enhanced the chance of identifying small differences in leptin levels.

**CONCLUSION**

The results of the present study do not support the existence of a significant difference in leptin levels between fibromyalgia patients and healthy controls.

**REFERENCES**


