Influence of acupuncture on leptin, ghrelin, insulin and cholecystokinin in obese women: a randomised, sham-controlled preliminary trial

Funda Güçel,1 Burak Bahar,2 Canan Demirtaş,3 Setenay Mit,3 Cemal Çevik3

ABSTRACT

Background  Obesity is an energy balance problem caused by overeating. Obesity treatment includes diet, exercise, behaviour treatment, pharmacotherapy and surgery; in addition, acupuncture is also an option.

Objective To investigate the effect of acupuncture on weight loss and whether a brief acupuncture treatment of 5 weeks can change circulating levels of leptin, ghrelin, insulin and cholecystokinin (CCK) in obese women.

Methods 40 women with a body mass index (BMI)>30 kg/m2 were equally randomised to either an acupuncture group or a sham (non-penetrating) acupuncture group and received treatment at LI4, HT7, ST36, ST44 and SP6 bilaterally. Both groups had two sessions of 20 min/week for a total of 10 sessions. Serum insulin, leptin, plasma ghrelin and CCK levels were measured by ELISA.

Results Acupuncture treatment decreased insulin and leptin levels and induced weight loss, together with a decrease in BMI compared with sham acupuncture. Furthermore, between-group analyses demonstrated increases in plasma ghrelin and CCK levels in subjects who received acupuncture treatment.

Conclusion These findings suggest that acupuncture may help to regulate weight owing to its beneficial effects on hormones such as insulin, leptin, ghrelin and CCK in obese subjects even after a few weeks of treatment.

INTRODUCTION

Obesity is a common health problem faced mostly in developed countries such as USA, Canada, Australia, and European countries but rates are increasing for developing countries as well. The risk of diabetes, hypertension, dyslipidaemia, cardiovascular disease and sleep apnoea are greater for overweight (body mass index (BMI)>25 kg/m2) and obese (BMI>30 kg/m2) individuals. There are various treatment options in practice such as diet therapy, regulation of physical activities, behaviour treatment, pharmacotherapy, surgical procedures and acupuncture.

Acupuncture is one of the treatment options in traditional Chinese medicine for a wide array of conditions and gaining attention in modern medicine. Acupuncture is thought to have been practised for several thousand years in China. Nowadays, even modern clinics use it for the treatment of various conditions such as obesity. NIH consensus conference statement (1998) on acupuncture stated that acupuncture shows promising results for several conditions.

Classic acupuncture points targeted in the treatment of obesity are Neiguan (P6), Fenglong (ST40), Liangmen (ST21), Guanyuan (R4), Zusanli (ST36), Tianshu (ST25) and Quchi (LI11). Besides these body points, there are also two points, generally targeted for appetite control, on the ear. In addition, to these generally recognised acupoints, an acupuncturist may use different points depending on his/her own experience. The evidence for the effect of acupuncture on weight loss is mixed: readers can find both supporting and refuting data.

Ghrelin is produced by P/D1 cells in the stomach, increases with hunger and decreases with satiety. Leptin, one of the products of adipose tissue, passes through the blood–brain barrier and reduces appetite. Ghrelin and leptin can be called counter hormones. Insulin is the main regulatory hormone of blood glucose levels and has been shown to decrease ghrelin levels. Cholecystokinin (CCK) secretion has been shown to decrease hunger. Because of these close interactions we aimed to evaluate the effect of acupuncture effect on these hormones and weight loss. We hypothesised that 5 weeks’ acupuncture treatment would cause weight loss accompanied by changes in the levels of the above-mentioned hormones.

SUBJECTS AND METHODS

Subjects

An acupuncture study was announced in a university hospital for employees and people attending for routine ‘wellness’ examinations. Female obese volunteers who wanted to be involved in this study underwent the selection process and 40 of these with BMI>30 kg/m2...
were chosen after routine medical examination. Subjects selected had normal physical examination findings and did not have hypertension, diabetes, nephropathy, heart failure and were not receiving any medication. Urn randomisation and parallel-group study design were used to randomly allocate subjects to either an acupuncture group or a sham acupuncture group. Urn randomisation was used because the study sample was small. It is an adaptive biased-coin design which decreases the probability of being assigned to an over-represented group. A computer program (SPSS 16—Statistical Package for the Social Sciences) was used for generation of allocation sequencing.

Ethics approval
The trial protocol was approved by Gazi University ethics committee and it met the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989 and 1996. All subjects provided informed consent after receiving information about the procedure and ethical considerations.

Acupuncture treatment
The acupuncture group received traditional Chinese-type general body acupuncture at LI4, HT7, ST36, ST44 and SP6 bilaterally after standard disinfection of the skin. Disposable stainless steel needles (25 mm long, 0.25 mm in diameter, Kingli, Lianghong Rd. Houzhai Town, Jiangsu, China) were applied through the skin to a depth of 5–10 mm. The stimulation was manual and the response sought was *de qi*. The remaining subjects were treated with sham acupuncture. The needles were not inserted but just applied under a tape at the same points. Both groups received two sessions of 20 min/week for a total of 10 sessions. Both treatments were performed by a certified acupuncturist. All subjects were asked not to follow dietary treatments, not to undergo heavy physical exercise and not to take supplementary medication. Morning fasting venous bloods were drawn at the beginning of first session and after completion of all sessions. Serum and plasma samples were collected after centrifugation and kept at −80°C until assays were performed. The study took place at Gazi University acupuncture outpatient clinic between 29 January 2009 and 7 January 2010.

Analytical methods
Serum insulin, serum leptin, plasma ghrelin and plasma CCK levels were measured by ELISA. Biosource Insulin Elisa Kit (Biosource Europe S.A., Rue du Bosquet, Louvain-La-Neuve, Belgium.), Biosource Leptin Elisa Kit (Biosource Europe S.A.), Biosource Human Unacylated Ghrelin Enzyme Immunoassay Kit (Biosource Europe S.A.) and Phoenix CCK Enzyme Immunoassay Kit (Phoenix Pharmaceuticals, Burlingame, CA, USA) were used.

Statistical analyses
Owing to the non-normal distribution of data, a Wilcoxon signed-rank test was used to determine statistical significance within acupuncture and sham groups for changes in weight and investigated hormones. Between-groups analyses were undertaken using Mann–Whitney U test of final mean values. SPSS 16 was used for statistical analyses and data were represented as mean±SD. A p value of <0.05 was considered statistically significant.

The sample size was not based on formal calculation as our sample was limited to those who responded to advertisements within the planned study period of 12 months.

RESULTS
Baseline data
The mean age of participants was 34.6±6.3 years for the sham acupuncture group and 36.8±7.8 years for the acupuncture group (p>0.05). Presham and preacupuncture groups showed no significant differences in weight, BMI, serum insulin and leptin levels. Mean plasma ghrelin and CCK levels were higher in the acupuncture group by 13.55 pg/ml (43%) and 0.29 ng/ml (44%), respectively. All participants successfully completed specified treatments without any dropouts or unintended outcomes. Results are shown in table 1 and figure 1.

Within-group analyses
The acupuncture group showed 2.9 kg (4%) mean weight loss, and the decrease in mean BMI was 1.43 kg/m² (4%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sham</th>
<th>Acupuncture</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.0±9.83</td>
<td>84.1±9.75</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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<td>34.46±4.79</td>
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<tr>
<td>Insulin (µIU/ml)</td>
<td>13.63±8.15</td>
<td>17.25±9.22</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>13.28±6.41</td>
<td>16.02±8.30</td>
</tr>
<tr>
<td>Ghrelin (pg/ml)</td>
<td>31.22±14.73</td>
<td>34.08±10.59</td>
</tr>
<tr>
<td>Cholecystokinin (ng/ml)</td>
<td>0.66±0.28</td>
<td>0.62±0.37†‡</td>
</tr>
</tbody>
</table>

Values are mean±SD. Wilcoxon sign-rank test for evaluation within groups, Mann–Whitney U test for evaluation between groups.

*p<0.05 (vs pre); †p<0.001 (vs pre); ‡p<0.001 (vs sham); §p<0.05 (vs sham).
In contrast, participants randomised to the sham acupuncture group did not show such changes. Mean serum insulin and leptin levels decreased by 6.87 μIU/ml (43%) and 3.32 ng/ml (25%), respectively, after acupuncture, while no change was seen in these variables after sham treatment. There was no change in plasma ghrelin and CCK levels for either the acupuncture or sham acupuncture groups.

**Between-groups analyses**

After 5 weeks of treatment subjects allocated to the acupuncture group had significantly lower weight and BMI than subjects in the sham acupuncture group. Furthermore, in the acupuncture group, mean serum insulin and leptin levels were lower than in the sham acupuncture group by 8.27 μIU/ml (48%) and 6.17 ng/ml (39%), respectively. The acupuncture group also demonstrated higher mean

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**Figure 1** Mean values for outcome measures in sham acupuncture group (1, pre; 2, post) and acupuncture group (3, pre; 4, post). Data are expressed as mean ± SE. *p<0.05 (vs pre); †p<0.001 (vs pre); A p<0.001 (vs sham); B p<0.05 (vs sham).
plasma ghrelin and CCK levels than the sham acupuncture group of 17.88 pg/ml (52%) and 0.37 ng/ml (60%), respectively.

**DISCUSSION**

In our study, we observed 2.9 kg weight loss, on average, after 5 weeks of general body acupuncture without a diet or exercise programme. Investigation of the literature shows similar results: an average decrease of 2.06 kg after 12 weeks with acupoint nerve stimulator at ST21, ST25, ST28, ST34 and SP4 on 16 volunteers who had no instructions to control their diets; an average weight loss of 5.0 kg after 3 months of auricular acupuncture on 110 obese patients; a mean weight loss of 4.1 kg after 20 days using electroacupuncture on 20 female patients given at both ear and body acupuncture points (LI4, LI11, ST25, ST36, ST44); and average weight reduction of 4.4 kg with 8 weeks of an auricular acupuncture, diet and exercise programme.

The effect of acupuncture on weight loss is thought to be through diverse mechanisms such as suppression of hunger; inhibition of gastric acid secretion; increase in plasma somatostatin, vasoactive intestinal peptide and β-endorphin; decrease in plasma gastrin; increase in the expression of the anorexigenic peptides α-melanocyte-stimulating hormone and cocaine and amphetamine-regulated transcript; and a decreased expression of orexigenic peptide neuropeptide Y.

Leptin is produced from fat cells proportionally to cell number and size, and is known to decrease body weight and appetite. It can also be detected in cerebrospinal fluid. We demonstrated a serum leptin decrease of 25% after acupuncture. Sham acupuncture did not produce such an effect. A study by Cabioğlu and Ergene of 20 women, who received both auricular and body acupuncture, showed a decrease in leptin levels. Kim et al using electroacupuncture of 100 Hz on normal rats fed freely showed an increase in leptin levels, but a study by You and Hung on obese rats demonstrated a fall in leptin levels. Carlson et al studied normal and severely obese women and demonstrated higher serum leptin levels and lower plasma ghrelin levels in the severely obese women. Considine et al reported that the leptin levels of normal weight and obese subjects were 7.5±9.5 ng/ml and 31±24.1 ng/ml, respectively, and suggested that obesity causes insensitivity to leptin. Whether the decrease in circulating leptin levels after acupuncture is due to a decreased production in the adipose tissue, as seen after weight loss, or an increased sensitivity to leptin remains to be elucidated, but it may be speculated that both mechanisms play a part in decreasing leptin levels. We think that one of the key effects of acupuncture is reversing leptin insensitivity, which is expressed as reduced leptin levels after treatment.

An increase in ghrelin is known to increase appetite and cause weight gain, and there is evidence that obese patients have lower plasma ghrelin levels and that a reduction in body weight raises plasma ghrelin levels. Wang et al suggest that in obese subjects, the normal function of ghrelin is impaired and electroacupuncture with an effective weight reduction can partly restore the diurnal rhythm. Hsu et al applied auricular acupuncture to obese women in a randomised controlled trial, which showed a significant increase in ghrelin and decrease in leptin levels after 6 weeks of treatment. Our 5-week acupuncture treatment also showed decreases in leptin and increases in ghrelin levels between groups.

Studies of the effect of acupuncture on insulin levels have mixed results, showing in different studies an increase and a decrease after treatment. Obesity, diabetes and insulin resistance are closely related. A hyperinsulinaemic euglycaemic clamp is the ‘gold standard’ for investigating insulin resistance and it can suppress plasma ghrelin concentrations in uncomplicated obesity. Maneras et al applied electroacupuncture to rats with polycystic ovary syndrome and using a euglycaemic clamp found no change in body weight, an increase in insulin sensitivity and a decrease in leptin gene expression in mesenteric adipose tissue compared with controls. The normal range of insulin was 2–20 mIU/ml for our method. In this respect, although the distribution of our data is non-parametric, we can state that preacupuncture levels of insulin were in the higher centiles and postacupuncture values decreased to the lower centiles. This suggests normalisation of insulin values and improved insulin sensitivity with acupuncture treatment, which is supported by our between-group analysis.

CCK is a neurotransmitter causing satiety after a meal by affecting the central nervous system, and hence it has close relationship with ghrelin. It can be said that ghrelin starts the meal while CCK ends it. Our between-group analysis documented a postacupuncture increase in CCK levels. Similarly, Lee et al observed decreased sphincter of Oddi motility and increased endogenous CCK levels in 11 patients with various biliary disorders during electroacupuncture at GB34. This effect did not occur in their control group, where acupuncture was performed at a different point (5 cm away from GB34). An animal experiment in a rabbit model demonstrated an increased number and amplitude of spikes of gastrointestinal myoelectrical activity, and a significant increase in serum CCK concentrations from 5 min before to 1 h after acupuncture. However, Lee et al showed contrasting findings, with CCK levels increasing during electroacupuncture, but CCK levels 5 and 10 min after stimulation not differing significantly from basal CCK levels. In summary, some studies demonstrate increased CCK concentrations during acupuncture while others show that CCK increases some time after acupuncture. Our study showed an increased fasting blood CCK level after a 5-week treatment.

Our study had some limitations. First, groups differed in ghrelin and CCK levels before receiving the designed treatment modality. We used a preferred allocation sequencing procedure which gave us sham and acupuncture groups equally distributed for age, weight, BMI, insulin and leptin levels, while ghrelin and CCK levels differed significantly. Second, our study population was relatively small and gender based so it will be of interest to perform
Provenance and peer review

Ethics approval

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Details of the each author with his/her contribution in this paper is as follows: FG: sample collection, writing manuscript; BB: writing manuscript, statistics; CC: supervisor.

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We conducted a sham-controlled, preliminary study of acupuncture for obesity. Second, we obtained only two blood samples from each subject; additional samples throughout the experiment might have provided more information about the influence of acupuncture.

Losing weight is a challenge in modern times and we are still searching for the most efficient method. Methods for the treatment of obesity have been evaluated through various projects and some have been shown to be scientifically effective. Choosing the right method is crucial for the patient. Doctors have options starting from diet to surgery. Recently, acupuncture has become another option for the doctor.6 7 There are many publications on the effect of acupuncture on weight loss and appetite hormones. In our study, we observed its effect on weight loss and its ability to decrease serum insulin and leptin levels and to increase ghrelin and CCK levels in obese women.

Contributors

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Competing interests

None.

Ethics approval

Gazi University Ethics Committee.

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