ARTICLE IN PRESS

General Hospital Psychiatry xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

General Hospital Psychiatry

journal homepage: http://www.ghpjournal.com

# The association between depression, weight loss and leptin/ghrelin levels in male patients with head and neck cancer undergoing radiotherapy

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ARTICLE INFO

*Article history:*
Received 22 January 2014
Revised 8 August 2014
Accepted 1 September 2014
Available online xxxx

*Keywords:*
Weight
Leptin
Ghrelin
Depression
Cancer

ABSTRACT

*Objective:* This study investigated the relationship between weight loss, depression and anxiety, and appetite hormones, leptin and ghrelin levels in patients with head and neck cancer (HNC), as well as the effect of radiotherapy and antidepressant treatment on weight and these hormones.
*Methods:* Forty male patients with HNC and twenty physically and mentally healthy male controls were recruited for the study. Psychiatric status was evaluated with clinical interview and psychometric tests. All patients received radiotherapy and antidepressant treatment with mirtazapine that was given to patients with psychiatric disorders. Serum leptin and ghrelin levels were measured pre- and post-treatment in the patients and once in the controls.
*Results:* There was no significant difference between the serum leptin and ghrelin levels of patients and controls. The leptin levels of the patients were decreased by radiotherapy. Eleven patients were diagnosed with major depressive disorder and adjustment disorder and were classed as depressive patients. Depressive patients were affected more by radiotherapy with respect to weight loss. The basal leptin levels of depressive patients were also lower than non-depressive patients and controls.
*Conclusion:* It seems that depression aggravated weight loss and, in addition, decreased leptin levels in cancer patients. Detection and treatment of psychiatric disorders may improve prognosis by preventing weight loss as well as by providing psychiatric treatment in cancer patients.



## 1. Introduction

Head and neck cancers (HNCs) are common cancers with a high mortality rate. Eating problems and weight loss is associated with mortality and morbidity in patients with HNC [1]. The etiology of malnutrition is multifactorial. Cancer-associated malnutrition can result from the effects of tumor and anticancer therapies such as chemotherapy and radiotherapy [2]. Psychological distress, including psychiatric disorders, is also associated with malnutrition. Baseline depression has been reported to predict malnutrition in HNC patients undergoing radiotherapy [3]. Studies have shown that patients with HNC display a significant level of psychological distress and psychiatric disorders such as depression and anxiety disorder at diagnosis, during treatment and for a long time following treatment [4–6]. Furthermore, patients with HNC were reported to be more frequently distressed than patients with other cancers [7]. The detection and treatment of psychiatric disorders is therefore important to reduce morbidity and mortality.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant that has antagonistic effects on adrenergic alpha2, 5-HT2 and 5-HT3, and H1 receptors. Sedation and increases in appetite and body weight are the most common side effects [8]. Mirtazapine is often preferred as an antidepressant because these side effects are advantageous in patients with cancer. Moreover, mirtazapine has been suggested to have efficacy in nausea and vomiting control in cancer chemotherapy and cachexia [9]. Clinical studies also showed the effectiveness of mirtazapine for nausea and insomnia as well as depression and anxiety in cancer patients [10,11]. Furthermore, antidepressant therapy with mirtazapine was shown to be associated with an increase in body weight, body fat mass and leptin level, and a decrease in ghrelin levels [12,13].

Adipocyte-derived leptin is an anorexigenic hormone that decreases food intake and increases energy expenditure [14]. Ghrelin is an orexigenic hormone produced by the gastrointestinal tract. Ghrelin induces weight gain through appetite control, energy balance and increasing food intake [15]. It has been reported that ghrelin is negatively associated with body fat mass and that leptin is positively associated with body fat [14,16]. Dysregulated stimulation of the leptin-activated pathways and/or blockade of the ghrelin-activated pathways causes

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http://dx.doi.org/10.1016/j.genhosppsych.2014.09.002
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cachexia [14]. Increased ghrelin levels and decreased leptin levels were reported in patients with a variety of cancers [17,18]. These hormonal changes have been associated with cancer-induced cachexia. Higher ghrelin levels [19,20] and lower leptin levels [21] were reported in cachectic patients compared with non-cachectic cancer patients. In consequence of these results, ghrelin was suggested as a therapeutic potential for cancer-induced cachexia [22] and radiotherapy-induced anorexia [23] because of the orexigenic and anti-inflammatory effect of ghrelin. There are a few clinical trials that showed the efficacy of ghrelin in patients with cancer anorexia [24].

Substantial evidence has shown impairment in leptin–ghrelin functioning in depression, although the results of studies about leptin and ghrelin levels and depression are controversial. Recent studies have focused on leptin resistance and impaired leptin action rather than changes in leptin levels in depression. It has been suggested that ghrelin increases as a response to chronic stress produced by depression and may play a role as an endogenous antidepressant [25].

In light of these studies, we aimed to investigate the relationship between weight loss and psychiatric disorders and leptin/ghrelin levels in patients with HNC. We hypothesized that cancer and/or its therapies induced weight loss that was aggravated by concomitant psychiatric disorders. Appropriate treatment of psychiatric disorders such as depression and anxiety may contribute to the improvement of nutritional status. Leptin and ghrelin, important hormones for the regulation of appetite and food intake, may play a role in this process. Therefore, weight, psychiatric status and serum leptin/ghrelin levels were investigated before and after radiotherapy in all patients, and before and after antidepressant therapy with mirtazapine in patients with a psychiatric disorder.

## 2. Method

### 2.1. Subjects

Forty male patients with non-metastatic HNC (localization in the larynx, pharynx, parotid gland, lip and oral cavity) were recruited for the study. The disease stage was stage III and IV (local invasion). Thirteen patients were postoperative. Exclusion criteria for patients were as follows: any endocrinological disease as judged from their clinical and biochemical examinations, having an alcohol or drug use disorder except smoking or receiving any hormonal therapy. Twenty physically and mentally healthy male controls were recruited from among volunteers and hospital staff. Exclusion criteria for the controls were the same as those for the patients, plus any present or past history of psychiatric disorder.

This study was approved by the local ethics committee. Written informed consent was obtained from all patients and controls after the study had been explained to them.

### 2.2. Procedure

The patients underwent psychiatric evaluation by means of clinical interview and psychometric tests by a psychiatrist before and after radiotherapy. The psychiatric disorders were diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 1994) criteria. The severity of symptomatology of depression was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D). The Hamilton Anxiety Rating Scale (HAM-A) was performed to evaluate anxiety. Eleven patients were diagnosed with major depressive disorder and adjustment disorder with anxiety and depressed mood before radiotherapy (RT). These patients, who were classed as depressive patients, were treated with mirtazapine 15–30 mg per day during the radiotherapy procedure for approximately 6 weeks. The patients did not use any other medication, such as another psychotropic or antihistaminic agent that may have an effect on weight. However, some of them received an antiemetic agent when necessary.

Weight and height measurement was performed in the patients pre- and post-treatment and in the controls. The body mass index (BMI) was calculated by dividing the weight (kilograms) by the squared height (meters) separately before and after the treatment. The formula was BMI=weight/(height×height).

Blood samples for leptin and ghrelin measurement were obtained in the morning after an overnight fast before and after RT in the patients and only once in the controls. Separated serums were stored at −70°C until analyzed. Serum leptin levels were determined by radioimmunoassay kits (DIAsource, Belgium). The sensitivity was 0.1 ng/ml and the intra- and inter-assay coefficients of variation were 4.4% and 5.0%, respectively. Serum ghrelin levels were also determined by radioimmunoassay kits (LINCO Research, USA). The sensitivity was 7.8 pg/ml and the within- and between-assay variations were 6.5% and 16.2%, respectively.

Patients were irradiated by using 6 MV Linear Accelerator Beams (Varian CDX 2300). RT was given through two parallel opposite lateral fields to the cervical lymph nodes as well as to the primary tumor sites and/or through the anterior field to the inferior cervical and the supraclavicular lymph nodes. It was given in 1.8–2.0 Gy/day doses 5 days a week by conventional fractionation (total 60–70 Gy by spinal cord protection at 46 Gy). All patients received standard dose and duration (approximately 6 weeks) RT.

### 2.3. Statistical analysis

The distributions of all variables were checked with the Shapiro–Wilk test. The comparison of age, weight and BMI in the patients and controls was performed with the independent samples *t* test; the comparison of these before and after treatment was performed with the paired samples *t* test. The nonparametric Mann–Whitney *U* test was used for analyses of psychometric tests scores and hormone levels between groups and the Wilcoxon test for comparison pre- and post-treatment measurements because of the abnormal distribution of these values. The analyses of subgroups according to presence of depression were performed using the same tests. To control the effect of age and BMI on leptin and ghrelin, adjusted leptin and ghrelin values were calculated with the formula taking BMI and age into account. The formula "adjusted hormone value=(hormone values×age×BMI)/(mean hormone values×mean age×mean BMI)" was used separately for both pre- and post-treatments and leptin and ghrelin. The change over time in leptin and ghrelin levels, namely delta leptin or ghrelin, was calculated by subtracting the post-treatment hormone value from the pre-treatment hormone value. The Spearman's correlation test was performed to investigate the relationships between leptin and ghrelin levels and clinical and demographical variables in the patients and controls separately.

## 3. Results

The mean age of the cancer patients (58.92±9.47) was higher than that of the controls (41.25±9.14) ($t$=6.893 $P$<.001). The weight and BMI of the patients were lower than those of the controls. The weight and BMI of the patients were further decreased by radiotherapy. There was no significant difference between the serum leptin and ghrelin levels of patients and controls. However, serum leptin levels of patients tended to be lower than those of the controls ($P$=.058). The leptin levels of the patients were decreased by radiotherapy and became lower than those of the controls (Table 1).

The weight and BMI of both non-depressive and depressive patients were lower than those of the controls both in pre- and post-treatments ($t$=4.769 $P$<.001, $t$=6.609 $P$<.001, $t$=3.290 $P$=.002 and $t$=5.194 $P$<.001 for non-depressive patient vs. controls; $t$=4.761 $P$<.001, $t$=6.192 $P$<.001, $t$=3.416 $P$=.002 and $t$=4.990 $P$<.001 for depressive patients vs. controls, in pre- and post-treatments, respectively). Radiotherapy decreased weight and BMI both in non-depressive patients ($t$=5.297 $P$<.001 and $t$=5.272 $P$<.001) and in depressive patients