Low Leptin Level Might Increase Susceptibility to *Mycobacterium Avium Complex* Infection

Noriaki Okada#, Tatsuo Kawashima*# , Kohji Shirai# and Yasuo Matsuzawa#

Department of Internal Medicine, Toho University Sakura Medical Center, Japan

#All authors equally contributed

Abstract

Object: Patients with *Mycobacterium avium complex* (MAC) infection without predisposing lung disease are predominantly elderly and often thin women. Malnutrition is an important cause of immune suppression and increases host susceptibility to infections. Recent evidence indicates that leptin functions as a signal in a feedback loop regulating food intake and body weight, is capable of modulating the immune responses. The objective of this study was to clarify the role of leptin in the infection of MAC.

Patients and Methods: We retrospectively analyzed the serum leptin concentration and other clinical characteristics in 41 patients with definitive primary pulmonary MAC and 28 normal female controls matched for age and body mass index.

Results: Serum leptin and TNF-α concentrations in the patient group (4.00 ± 2.40 ng/ml and 1.17 ± 0.42 pg/ml, respectively) were significantly lower than those in the control group (4.86 ± 3.90 ng/ml and 1.33 ± 0.97 pg/ml) (p=0.043 and 0.021). No significant differences in other clinical characteristics were observed between two groups.

Conclusion: These findings suggest that leptin is one of the defense mechanisms against MAC infection in individuals without predisposing lung disease.

Keywords: Leptin; Mycobacterium avium complex; Malnutrition; Immunosuppression

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Introduction

The incidence of pulmonary disease caused by *Mycobacterium avium complex*(MAC) infection in patients without predisposing lung diseases such as pulmonary tuberculosis, bronchiectasis and pneumoconiosis [1-3], or in immunocompromised hosts such as those with Acquired Immunodeficiency Syndrome (AIDS) [4] has shown a trend of increase [5,6]. MAC is a ubiquitous environmental microorganism, especially in water habitats [7]. Despite universal exposure to this organism, the occurrence of MAC disease is rare. Therefore, normal host defense must be effective enough to prevent the infection. The MAC-infected patients are predominantly thin, nonsmoking, elderly women with abnormal findings such as multiple small nodules and bronchiectasis on chest radiographs and/or chest CT scans [8,9].

There are several unresolved issues regarding the characteristics and development of MAC infection in individuals without predisposing lung disease or immunodeficiency, including the reason for its prevalence in some thin and elderly women having abnormal radiological features.

Malnutrition is an important cause of immunosuppression and increases host susceptibility to infectious disease [10]. Recent evidence indicates that leptin is capable of modulating the immune responses, and that serum leptin concentrations are regulated by the nutritional status, especially obesity [11,12].

In the present study, we retrospectively analyzed the clinical features, laboratory data, and leptin serum concentration in patients with MAC infection who had no predisposing lung disease or immunodeficiency.

Methods

Subjects

We studied 41 female patients who visited Toho University Sakura Medical Center for evaluation
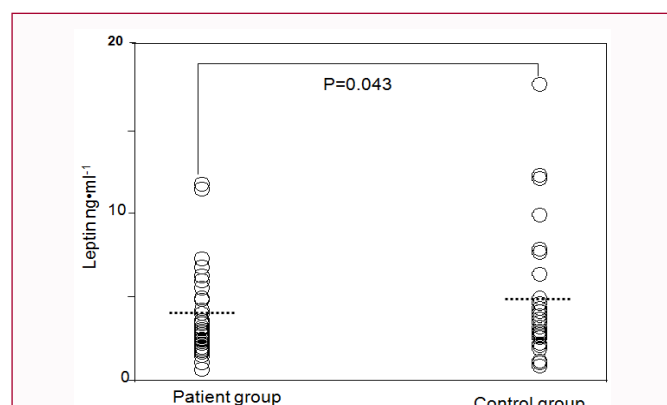
Figure 1: Leptin concentrations in the patient group and control group.Dotted line shows the mean value in each group.
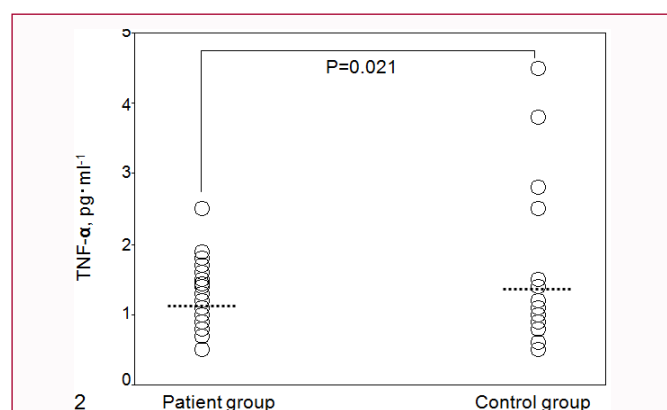

Figure 2: TNF-α concentrations in the patient group and control group. Dotted line shows the mean value in each group.

Table 1: Patient Characteristics.

	Patient Group # (n=41)	Control Group (n=28)	p-value
Age, yr	65.8 ± 10.4	68.7 ± 9.8	0.775
BMI, kg/m²	18.3 ± 2.3	18.9 ± 1.8	0.416
Leptin, ng/ml	4.00 ± 2.40	4.86 ± 3.90	0.043
TNFα, pg/ml	1.17 ± 0.42	1.33 ± 0.97	0.021
NK cell activity, %	34.4 ± 15.3	35.6 ± 16.8	0.358
Total protein, g/dl	7.64 ± 0.55	7.34 ± 0.51	0.081
Albumin, g/dl	4.20 ± 0.41	4.34 ± 0.51	0.085
Cholinesterase	328 ± 78	308 ± 74	0.728
Immunoglobulin G, mg/dl	1513±396	1251 ± 320	0.369

Data are mean ± SD. BMI: Body Mass Index; #, Patient Group was diagnosed with primary pulmonary mycobacterium avium-intracellulare infection (MAI) upon satisfying all of the diagnostic criteria for nontuberculous mycobacterial disease proposed by the American Thoracic Scoiety, including the bacteriologic criteria.

(ELISA) and test for NK cell activity in blood were performed in a central laboratory (SRL, Tokyo, Japan). All samples were assayed in duplicate, and pooled human plasma samples were included to assess variability.

Statistical analysis

Data analysis was performed using SPSS software for Windows (SPSS Inc. Chicago, IL, USA). Continuous data are expressed as mean ± SD. Differences between the patient group and control group were examined using Student's unpaired t-test. A p-value less than 0.05 was considered significant.

Results

The clinical characteristics of the two groups are shown in Table 1. The patient group ranged in age from 55 to 86 years, with an average of 68.5 years. The control group ranged in age from 54 to 88 years, and the average was 68.7 years. Serum leptin and TNF-α concentrations in the patient group (4.00 ± 2.40 ng/ml and 1.17 ± 0.42 pg/ml, respectively) were significantly lower than those in the control group (4.86 ± 3.90 ng/ml and 1.33 ± 0.97 pg/ml) (p=0.043 and 0.021) (Figures 1 and 2), whereas the mean BMI was not significantly different between the patient group (18.3 ± 2.3 kg/m²) and the control group (18.9 ± 1.8 kg/m²) (p=0.416). No significant differences in other clinical characteristics were observed between the patient and control groups. NK cell activity in blood was not significantly different between two groups (p=0.358).

Discussion

Malnutrition is an important cause of immune suppression and increases host susceptibility to infectious diseases [10]. The effects of nutritional deficiencies on tuberculosis could result in the impairment of several important effecter mechanisms of the immune system, including cellular immunity [13,14].

Leptin affects both nutritional status and immunity, and strongly correlates with BMI and adiposity [11,12]. Leptin is an adipokine that plays an important role in the regulation of energy homeostasis by transmitting signals regarding peripheral lipid energy stores to the satiety center in the brain [15]. Circulating level of this adipocyte-derived hormone correlates with total fat mass; the level declines during periods of energy deprivation [16,17] and increases during inflammation and infection [18,19]. Leptin has been demonstrated to play an important role in T cell-mediated immune responses

of respiratory disease between January 1999 and March 2008. All patients were nonsmokers. Abnormal findings such as multiple small nodules and bronchiectasis on chest radiographs and/or chest CT scans suggested MAC infection. The patients were subsequently diagnosed with primary pulmonary MAC upon satisfying all the diagnostic criteria for nontuberculous mycobacterial disease proposed by the American Thoracic Society (ATS) [8] including the bacteriologic criteria. All patients had no other distinct lung diseases, as judged by the medical history and previous chest radiographic and/or CT findings, which in most cases, were performed as part of a complete examination. The patients also had no HIV infection. We recruited 28 female nonsmoking volunteers as normal controls, who were matched for age and BMI with the patients. All volunteers had no previous significant diseases and no HIV risk factors, and the findings of chest radiography and chest CT were normal.

This study was approved by the guidelines of the Institutional Review Board at our institution, and written informed consent was obtained from all patients and normal female volunteers.

Laboratory data

The following clinical data were collected from each patient and normal female volunteer: age; height; body weight; Body Mass Index (BMI); routine laboratory tests including total protein, albumin and cholinesterase; as well as serum indicators of immune response including immunoglobulin G, serum leptin concentration, serum tumor necrosis factor (TNF-α) concentration and NK cell activity in blood. Assays for serum leptin and TNF-α concentration

[20]. Cells from *ob/ob* mice (leptin-deficient) show defective mixed lymphocyte reactions, with poor generation of INF-γ and increased IL-4 production. *In vitro* treatment of cells from *ob/ob mice* with leptin reverses mixed lymphocyte reaction defects, leading to vigorous secretion of INF-γ and blunting of IL-4 secretion [14]. In addition, leptin enhances the secretion of TNF-α, IL-6 and IL-12 by peritoneal macrophages, as well as IFN-γ by T cells [21,22].

On the other hand, the principal defense mechanism of MAC infection is the activation of infected macrophages by type 1 cytokines such as TNF-α and interferon-γ (INF-γ) [23,24]. These proteins are produced by antigen-specific type 1 helper T cells (Th1 cells) and natural killer (NK) cells, and they bind to their receptors at the macrophage surface [25,26]. The production of INF-γ by Th1 and NK cells is regulated by another cytokine, interleukin-12 (IL-12) [27]. IL-12 is produced by antigen-presenting cells such as macrophages, monocytes and dendritic cells after activation of Toll-like receptors on these cells by bacterial ligands [28,29].

Despite the progress made in the studies of defense mechanism of MAC infection, there are some unresolved issues regarding the characteristics and development of MAC-infection in individuals without predisposing lung disease or immunodeficiency. One of the issues is the reason for its prevalence in some thin and elderly women having abnormal radiological features. In our present study, we investigated the differences in nutritional status and immune functions between patients with definitive primary pulmonary MAC and age- and BMI-matched normal female controls.

In our study, the mean BMI (18.3 ± 2.3 kg/m^2) and age (68.5 ± 10.4 years) in the patient group confirmed that the patients infected with MAC were thin (BMI <20) and elderly women, in agreement with previous reports [8,9]. One of our main findings is that serum leptin and TNF-α concentration in the patient group were significantly lower than those in the control group, while the mean BMI in the patient group was not significantly different from that in the control group. Our results suggest that in patients infected with MAC, malnutrition induces a greater decrease in serum leptin concentration than in normal subjects, leading to greater decline in serum TNF-α concentration and increased susceptibility to MAC infection. Furthermore, serum leptin concentration may be associated with serum TNF-α concentration but not with NK cell activity.

We measured other markers of nutritional status such as serum total protein, albumin, cholinesterase and immunoglobulin. However, no significant differences in the above markers were observed between the patient group and control group. Our data thus suggest that leptin is one of the defense mechanisms of MAC infection in patients without predisposing lung disease. Current research suggests that leptin is both a satiety-regulating hormone and a cytokine-like immune regulator. Thus, eating disorders may cause decreased leptin secretion in patients with primary pulmonary MAC infection without predisposing lung disease or immunodeficiency.

In conclusion, the present study suggested that leptin is one of the defense mechanisms of MAC infection in individuals without predisposing lung disease. Further studies are needed to clarify the role of leptin in patients with primary pulmonary MAC infection with neither predisposing lung disease nor immunodeficiency.

Summary at a Glance

We studied the role of leptin in *Mycobacterium avium complex* (MAC) infection. Serum leptin in infected patients was significantly lower than that in controls, suggesting that leptin may be one of the defense mechanisms against MAC infection.

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