

Regulation of Interleukin-6 and Leptin in Schizophrenia Patients: A Preliminary Analysis

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Objective: Immune-inflammatory mediators play a pivotal role in brain signaling and have been increasingly associated with the pathophysiology of schizophrenia. Many studies have indicated an increased level of immune-inflammatory interleukin-6 (IL-6) in schizophrenia. IL-6 is a well-known chief stimulator of inflammation. Of late leptin has also been implicated in the inflammatory pathway of schizophrenia. In this study we measured and compared serum levels of IL-6 and leptin in patients with schizophrenia to healthy controls, and investigated the relationship between IL-6 and leptin.

Methods: Serum IL-6 and leptin were determined in 20 patients diagnosed with schizophrenia and in 19 healthy controls matched by gender, age and body mass index (BMI) using commercial Bioplex assays.

Results: Using Mann-Whitney U-test, significantly increased IL-6 levels were found in the patients but there was no significant difference in leptin levels though a trend towards higher leptin was observed in the patients. Spearman correlations did not show any correlation between IL-6 and clinical variables except antipsychotic dosage. Leptin significantly correlated with gender and BMI. A large effect size correlation was observed between IL-6 and leptin in the patients but not in the controls. Multiple regression analysis performed on patients, after adjusting for gender and BMI, revealed there was no significant association between IL-6 and leptin.

Conclusion: IL-6 and leptin levels may reflect the chronic inflammatory state associated with schizophrenia but further evaluation is required. Also, it is important to consider the confounding effects of obesity in any examination of relationships between groups with regard to cytokines and adipokines.

KEY WORDS: Inflammation; Immune; Psychotic disorders; Adipokines.

INTRODUCTION

The pathogenesis of schizophrenia is widely believed to be based on gene-environment interactions. Genetic studies have suggested that genes related to immune-inflammatory response contribute to the pathophysiology of the disease.^{1,2} Furthermore, epidemiological and animal studies have indicated that adverse environmental factors such as an unhealthy family environment, a stressful life event, pre-natal and peri-natal exposure to adverse factors increase the risk of developing schizophrenia.³ Altered immune-inflammatory cytokine dysregulation has been postulated as a possible common pathway to both genetic

and environmental components of schizophrenia that occur either in early life or during the acute state in adult life.^{1,4}

Inflammation is an adaptive body response which can be divided into acute inflammation, the initial localized body response to infection or injury which is essential for tissue repair and recovery⁵ and chronic inflammation, a persistent phenomenon which replaces acute inflammation when the agent causing the inflammation cannot be eliminated. Chronic inflammation can last for several months and even years; it can be detrimental as it could lead to damage of non-infected, healthy and unwounded tissue.^{6,7} While a number of immune-inflammatory cytokines have been identified, interleukin-6 (IL-6), a proinflammatory interleukin is the chief stimulator of the acute phase response in inflammation which leads to behavior, physiologic, biochemical and nutritional changes during an inflammatory state.⁸ IL-6 exerts stimulatory effects on T and B cells facilitating the transition from acute to chronic state inflammation by altering the immune sys-

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tem-changing the nature of leucocyte infiltration from neutrophils to monocyte/macrophages.⁵⁾ Studies have indicated an increased level of IL-6 in schizophrenia, and a genetic polymorphism in the IL-6 gene.⁹⁾

Apart from IL-6, leptin, primarily an adipokine, initially discovered to function as a satiety factor has been indicated to function as a proinflammatory cytokine¹⁰⁾; and studies have reported altered leptin levels in schizophrenia patients.¹¹⁾ Leptin levels are rapidly increased in response to many acute phase cytokines including IL-6. Leptin is structurally related to the cytokine family and its signal-transducing pathway is also regulated as a cytokine in response to infection and inflammation.¹²⁻¹⁵⁾ The proinflammatory nature of leptin is supposedly beneficial during acute infections in both rodents and human, but chronically the proinflammatory shift has been suggested to be deleterious.¹⁶⁾ More recently, leptin has been recognized to be involved in brain functions such as neuronal development and survival; and various aspects of behavior and cognition which are disturbed in schizophrenia.¹⁷⁾ There exists evidence for an association between leptin, cognition and behavior in both rodent and human studies. Leptin has also been reported to modulate activity of mesolimbic dopaminergic neurons in the hypothalamus, which is implicated in schizophrenia.¹⁸⁾

IL-6 and leptin are both secreted by adipose tissue and hence their relationship with obesity has been previously reported. As much as one-third of circulating IL-6 has been attributed to adipose tissue secretion, with macrophages being the major contributor.^{19,20)} Additionally, leptin is secreted by adipocytes to down-regulate appetite.²¹⁾ Increasingly, studies indicate that obesity and being overweight are associated with immune-competence alterations.²²⁾ Increased bioavailability of active inflammatory molecules, such as IL-6 and leptin, with local and systemic effects, may bring about a vicious cycle, contributing to the overall chronic inflammatory state in obese individuals. Impaired immune function in excess adiposity has been related to insulin resistance,^{23,24)} poor response to and higher incidence of infection,²⁵⁾ all of which negatively impacts health.

While there are suggestions that IL-6 and leptin are closely associated in obesity, there is a paucity of studies that examine the relationship between IL-6 and leptin in psychiatric illnesses including schizophrenia. Limited studies have provided inconsistent findings examining the link between IL-6 and leptin. Trujillo *et al.*²⁶⁾ showed that IL-6 increased leptin production; while others concluded that IL-6 inhibited or had no effect on leptin production in human adipocyte cultures.^{27,28)} Therefore, in this study,

our objective was to evaluate and compare serum levels of IL-6 and leptin in patients with schizophrenia to healthy controls, and to investigate the relationship between IL-6 and leptin.

METHODS

Subjects

Patients diagnosed with schizophrenia above 21 years old were recruited from the Institute of Mental Health in Singapore and matched with healthy controls by gender, age and body mass index. Patients with a history of neurological disorder or head injury; and controls with a history of psychiatric illness were excluded from the study. Participants who reported known immune disorders were excluded from this study. Only participants who were capable of providing written informed consent were recruited. Ethics approval was provided by the National Healthcare Group Domain Specific Review Board.

Demographic and medical information were collected from all participants. Diagnosis of schizophrenia was ascertained on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders 4th edition, text revision (DSM-IV-TR) Axis I Disorders. Weight and height was obtained from all participants and their body mass index (BMI) computed. Clinical symptoms were assessed on the Positive and Negative Syndrome Scale (PANSS).²⁹⁾ Current antipsychotic doses were converted into chlorpromazine equivalents.^{30,31)}

IL-6 and Leptin Measurements

Venous blood was collected from all study participants into serum separating tubes (SST). Immediately after collection, blood samples were allowed to coagulate at room temperature for approximately 30 minutes. Subsequently, serum samples were collected through 10 minutes centrifugation at 4°C using a clinical centrifuge (Hettich, Tuttlingen, Germany). Serum IL-6 and leptin were measured using commercially available Bioplex IL-6 and leptin assays (Bio-Rad, Hercules, CA, USA). Briefly, serum samples were diluted 1 : 4 in sample diluents provided and ran in duplicates according to the instruction's manuals. The sensitivity of the kits was 2.6 pg/ml and 3.1 pg/ml for IL-6 and leptin respectively.

Statistical Analysis

Data was analyzed on PASW Statistics software ver. 18.0 (IBM Co., Armonk, NY, USA). Descriptive statistics were tabulated for the patient and control groups.

Statistical significance was set at $p < 0.05$ and was examined using chi-squared test for categorical variables and non-parametric test for continuous variables. Serum IL-6 and leptin between patients and healthy controls were compared using Mann-Whitney U -test. Spearman correlation coefficients were calculated to examine the relationships between IL-6, leptin and clinical variables. Multiple regression analysis was used to examine the relationship between IL-6 and leptin after adjusting for potential confounders.

RESULTS

Our study comprised of 20 patients and 19 controls. Table 1 shows the demographic and clinical characteristics of the study participants. The patient and control groups were matched by age, sex and BMI. Serum IL-6 and leptin levels in patient and control groups are shown in Fig. 1. Serum IL-6 levels of the patients ($2.4 \text{ pg/ml} \pm 0.6 \text{ pg/ml}$) were significantly higher compared to controls ($0.9 \text{ pg/ml} \pm 0.2 \text{ pg/ml}$) ($p=0.003$). Serum leptin levels were higher in the patients ($6.1 \times 10^3 \text{ pg/ml} \pm 1.6 \times 10^3 \text{ pg/ml}$) compared to the controls ($5.2 \times 10^3 \text{ pg/ml} \pm 1 \times 10^3 \text{ pg/ml}$), but did not reach statistical significance ($p=0.930$). In the patient group, serum IL-6 was positively correlated with leptin ($r=0.52$, $p=0.02$) while in the control group there was a weaker and non-significant association ($r=0.39$, $p=0.127$) shown in Figs. 2 and 3. IL-6 correlated significantly with antipsychotic dose ($r=0.502$, $p=0.024$), but there was no

significant correlation with gender, age, age of illness onset, BMI, smoking status, duration on illness and psychiatric treatment and type of antipsychotic. Leptin correlated positively with gender ($r=0.511$, $p=0.021$) and BMI ($r=0.475$, $p=0.034$). In the multiple regression analysis performed on patients, after adjusting for gender and BMI, there was no significant association between IL-6 and leptin (Beta=0.012, $p=0.949$).

DISCUSSION

In the present study IL-6 and leptin were found to be comparatively higher in the patient group, though leptin did not reach statistical significance. Within the patient group IL-6 correlated positively with antipsychotic dose, but not the other clinical variables; while leptin correlated positively with gender and BMI. Conflicting findings between these two proinflammatory cytokines and clinical variables have been reported in schizophrenia. Circulating levels of IL-6 have been reported to show a positive correlation with age,³²⁻³⁴ duration of illness^{33,35} and age of onset³⁶; while some reported nil or a contrasting relationship.³⁶⁻³⁹ Reported gender differences have also been inconsistent.^{33,34,36,40} The inconsistencies in study findings could be a result of differences in sample size, manner in which biological samples were collected and analyzed, assay methods, and potential confounders such as age, gender, BMI and smoking status. Nonetheless, leptin's positive associations with gender and BMI have been consistent with previous reports.¹¹

Table 1. Demographic and clinical information of study participants

	Total (n=39)	Control (n=19)	Patient (n=20)	p-value
Demographics				
Gender (male/female)	25 (64.1)/14 (35.9)	11 (57.9)/8 (42.1)	14 (70)/6 (30)	0.431*
Age (yr)	36.7 \pm 6.9	38 \pm 6	35.6 \pm 7.6	0.293 [†]
Body mass index (kg/m ²)	24.8 \pm 4.1	24.4 \pm 3.5	25.1 \pm 4.7	0.606 [†]
Clinical variables				
Age of onset (yr)			24.9 \pm 6	
Duration of illness (yr)			10.4 \pm 7.2	
PANSS total			38.4 \pm 7.5	
PANSS positive subscale			10.2 \pm 4.1	
PANSS negative subscale			9 \pm 3.3	
Type of antipsychotic				
Typical			9 (45)	
Atypical			8 (40)	
Typical and atypical combined			3 (15)	
Additional therapy				
Anticholinergic			10 (50)	
Selective serotonin re-uptake inhibitor			5 (25)	
Benzodiazepines			2 (10)	
Antipsychotic daily dose in chlorpromazine equivalents (mg)			318 \pm 375	

Values are presented as number (%) or mean \pm standard deviation. *Chi-squared test, [†]Mann-Whitney U -test.

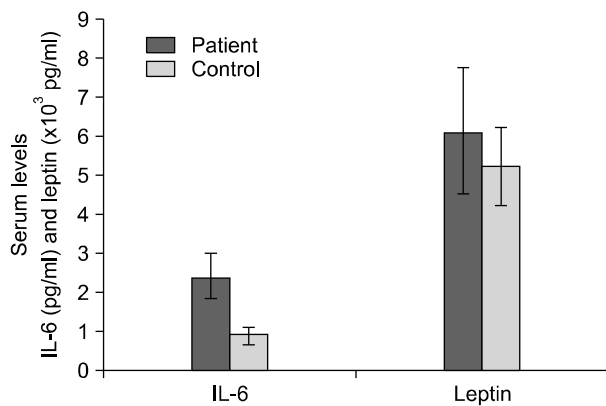


Fig. 1. Data is presented as mean±standard error. Interleukin-6 (IL-6) levels were significantly higher in the patient group ($p=0.003$) while no significant difference was found in leptin levels between patient and control groups ($p=0.930$).

A large effect size correlation between IL-6 and leptin in schizophrenia patients was seen in this study. After adjusting for BMI, a surrogate measure for adiposity, there was no longer any association between IL-6 and leptin. This suggests that the relationship between IL-6 and leptin is moderated by obesity. Obesity has consistently been linked to increased inflammation.⁴¹⁾ Adipose tissue has been found to be an active participant modulating immune-inflammatory responses in physiological and pathological processes.⁴²⁾ Increased adipose tissue activity could contribute to the inflammatory component of schizophrenia. Moreover, physical inactivity, unhealthy dietary choices, smoking and stress, which are commonly seen in schizophrenia patients, have all been associated with low grade inflammation independent of adipose tissue activity.⁴³⁻⁴⁵⁾ In response to infection or inflammatory signals, adipose tissue has been shown to regulate production of acute phase proteins including IL-6, and potential inflammatory modulators such as leptin.⁴⁶⁾ Therefore, any examination of relationships between groups with regard to cytokines and adipokines would need to take into consideration the confounding effects of obesity.

The present study found IL-6 to be positively correlated to antipsychotic dose. Though the effect of antipsychotic medications on cytokines have been previously reported, the findings have been inconsistent; with some reports of a positive association,^{47,48)} a negative association^{37,49-51)} and also, absence of any such relationship.^{35,39,52,53)} Antipsychotics, specifically atypical antipsychotics have been known to increase rates of obesity, which leads to upregulation of IL-6 and leptin.⁵⁴⁾ Though leptin has been purported to have neuroprotective properties; however, in the case of antipsychotic-induced leptin resistance and in obesity, this neuroprotective role

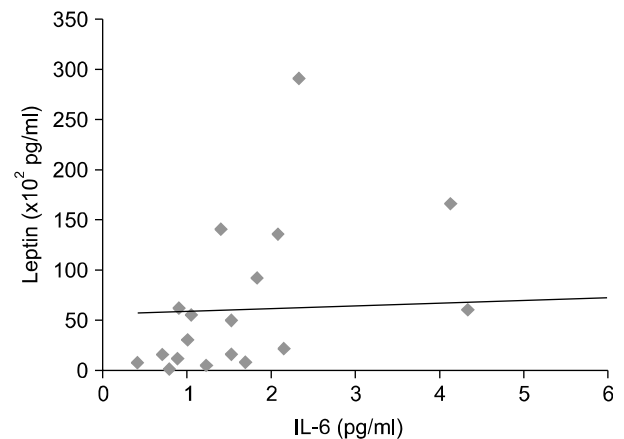


Fig. 2. Scatterplot of serum leptin and interleukin-6 (IL-6) in patients. Significant positive association was observed between IL-6 and leptin in the patient group ($r=0.52$, $p=0.02$).

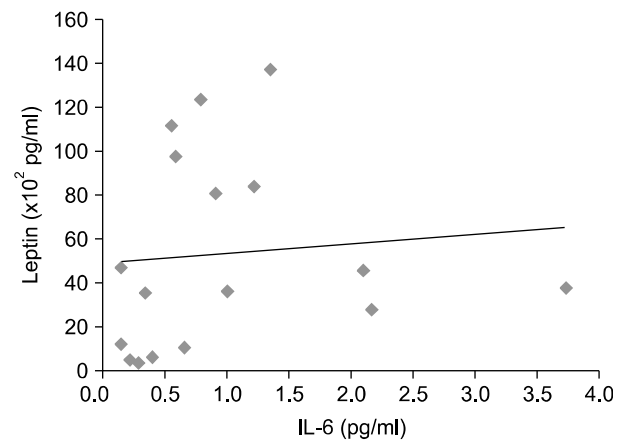


Fig. 3. Scatterplot of serum leptin and interleukin-6 (IL-6) in controls. A weaker and non-significant association was observed between IL-6 and leptin in the control group ($r=0.39$, $p=0.127$).

appears unclear.^{55,56)} Therefore, it was suggested that changes in cytokine levels associated with antipsychotic treatment may be secondary to weight gain.⁵⁷⁾

In the control group, no correlation was found between IL-6 and leptin. Studies have reported lower IL-6 and leptin levels in healthy controls compared to patients with schizophrenia.^{58,59)} Therefore, in the absence of an inflammatory condition or stimuli, and at basal levels, it is unsurprising that IL-6 and leptin levels would be low, and poorly correlated.

The advantages of the study were that it was conducted at a single site which eliminates any potential inter-site variation with regard to venous blood collection and laboratory processes. All participants were carefully assessed for presence of schizophrenia in cases and absence of psychiatric disorders in controls.

The results reported in the present study need to be interpreted in the context of certain limitations. The small sample size in this study is one limitation to consider that might have led to the negative associations between IL-6, leptin and clinical variables. Other considerations include the chronicity of the illness and treatment, which might have affected expressions of IL-6 and leptin. In addition, the cross sectional nature of the study did not permit us to study temporal relationships between IL-6, leptin and development of obesity in schizophrenia.

In conclusion, elevated serum levels of proinflammatory cytokines such as IL-6 and leptin may reflect a chronic inflammatory state in schizophrenia and leptin could play an important part contributing to the immune-inflammatory milieu. Further studies are warranted to provide insights into the roles of proinflammatory cytokines in the pathophysiology of schizophrenia, as well as in the development of metabolic disorders in schizophrenia.

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