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BRIEF REPORT

The relationship between weight change and C3 complement levels in patients with anorexia nervosa

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ABSTRACT

Objective: Anorexia Nervosa (AN) affects the entire body with serious medical conditions and has the highest mortality rates in any psychiatric disorder. These medical abnormalities are reversible after weight gain and resolution of the underlying anorectic state. The role of the immune system in the development and maintenance of AN is apparently underestimated. Changes in the complement system, particularly C3 in AN, are not well understood. This study was designed to evaluate changes in body weight and complement C3 levels.

Method: This study was designed as a prospective study on 12 female AN patients. Serum samples were taken biweekly for 4 times. The serum levels of complement C3 levels were quantified and correlated with the body mass index (BMI). Repeated measures of ANOVA were used to determine changes in BMI and C3 complement levels. A generalized estimating equation (GEE) analysis was used to determine the relationship between BMI and complement C3 levels over time.

Results: An increase in C3 levels was observed in the analysis of the data according to the increase in body weight of the patients as a result of eating of AN patients. There was a significant increase in C3 levels (p=0.042) and BMI levels of the patients (p=0.01). The increase in BMI was followed by the increase in C3 level. BMI increases over time were statistically correlated with changes in C3 levels.

Conclusion: Increasing C3 levels with increasing BMI during the treatment process are parallel. Complement 'C3' serum levels potentially serving as a guide for monitoring the refeeding process also could be a useful marker for determining and monitoring the treatment success in AN.

Keywords: Anorexia nervosa, body mass index, complement levels, weight change

INTRODUCTION

Anorexia Nervosa (AN) appears to affect the whole body with serious medical conditions and has the highest mortality rate in any psychiatric disorder (1,2). The degree of metabolic and physiological changes that occur depends on the duration and severity of intake reduction and the amount of weight loss (3). The treatment process is long and difficult due to serious medical conditions (1). However these medical abnormalities can be reversed after weight gain and reso-lution of the underlying anorectic condition. To date, there is no definitive marker that monitors the treatment process or progression of the disease (4,5).

The pathogenesis of an increasing number of chronic diseases has been attributed to effects of the immune system, the role of immune system in the development and maintenance of anorexia nervosa is apparently not

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sufficiently appreciated, but while immunological changes are diffi-cult to explain due to secondary malnutrition alone, the exact pathogenesis of these immunolog-ical changes in anorexia nervosa is unclear, the immune system may actually be causative in the pathogenesis and maintenance of anorexia nervosa (6). Traditional cascade pathways and repre-sents the first-line defense mechanism against pathogens (7-10). Most of the complement proteins are synthesized by the liver and macrophages (7,9,10). Recent studies show that adipose tissue is the production site of some complement proteins, suggesting links between the energy balance system and the immunity (11-15). Studies on complement levels with low body weight show that malnutrition has been associated with multiple immunologic deficits and decreased complement levels, particularly 'C3' and factor B (16-22). Although it is unclear that low com-plement levels are caused by impaired production or chronic activation of the complement cas-cade by recurrent infections (21,23). Moreover, AN has traditionally been viewed as a malnourishment disease, patients do not usually have superimposed inflammatory states, such as infection or malignancy, which raise the levels of certain complement proteins (24,25). Reports of complement components of a few AN patients, especially alternative pathways may be insuf-ficient, but this has not been systematically studied (26-28).

We hypothesized that weight loss in AN results in C3 consumption, and serum C3 levels would increase with weight gain over the course of treatment, and therefore C3 levels may be a useful marker for monitoring the treatment success in AN.

Even the most anorexic patients may present with normal laboratory values, underscoring the need for a new sensitive biomarker. This study was designed to evaluate complement levels in patients with anorexia nervosa, and to determine whether complement serum levels may repre-sent a useful marker for determining and monitoring the disease. Therefore, this study was de-signed to evaluate changes of complement C3 levels with body weight changes in AN.

METHOD

Patients

Twelve AN patients were recruited from the outpatient psychiatry clinic of Sakarya University Faculty of Medicine.

The inclusion criteria were as follows:

(i) 18 years of age or older;

(ii) AN diagnosis.

The exclusion criteria were as follows:

(i) the presence of acute (e.g., infections, diseases) or chronic disease affecting complement levels (e.g., hypertension, diabetes, liver disease, kidney diseases, current thyroid dysfunction, or neurological disease);

(ii) existing comorbid Axis I disorders.

The ethics committee of Sakarya University Faculty of Medicine was obtained. All procedures were performed after participants had demonstrated adequate understanding and provided written informed consent. The patients received diet and appetite-enhancing medication.

Blood Sampling

Blood samples were obtained every 2 weeks in the morning during the fasting period. Bodyweight and C3 levels were assessed every two weeks. Patients were under acute phase treatment (weight gain period) followed up for 6 weeks, so each patient has 4 (beginning, second, fourth, and sixth week) laboratory and weight results.

Statistical Analysis

Key characteristics of the study participants are defined by mean and standard deviation (SD) or percentages. Repeated measures of ANOVA were used to determine changes in body mass index (BMI) and C3 complement levels. The Generalized Estimating Equations procedure extends the generalized linear model to allow analysis of repeated measurements to determine the relationship between BMI and complement C3 level over time for the anorexia nervosa patients. Differences were considered significant when $p<0.05$.

RESULTS

All patients were women with a mean age of 23.4 (SD=6.5), and a mean height of 159 cm (SD=4.3). The initial mean body mass of BMI of patients: 14.96 (SD=1.70) and C3 levels 0.88 g/lt (SD=0.19), at the second week of treatment average BMI: 16.01 (SD=1.76) and C3 levels 0,96 g/lt (SD=0.21), at the fourth week of treatment average BMI: 16.86 (SD=2.06) and C3 levels 1.03 g/lt (SD=0.33), at the end of treatment (sixth week) average BMI: 17.38 (SD=1.77) and C3 levels 1.16 g/lt (SD=0.31) of the twelve patients. Repeated measures of ANOVA were used to determine changes in BMI and C3 complement levels over time. There was a significant increase in C3 levels ($p=0.042$) and BMI levels of patients ($p=0.01$). The increase in BMI was followed by an increase in C3

Table 1: BMI and C3 levels over time

	BMI (kg/m²)		C3 (g/lt)	
	Mean	**SD**	**Mean**	**SD**
0th week	14.96	1.70	0.88	0.19
2th week	16.01	1.76	0.96	0.21
4th week	16.86	2.06	1.03	0.33
6th week	17.38	1.77	1.16	0.31

BMI: Body mass index, SD: Standard deviation

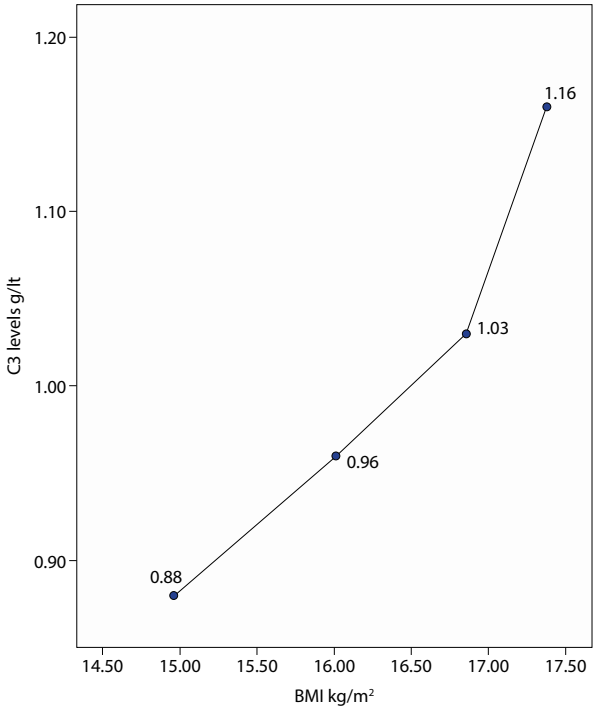

Figure 1. Correlation between BMI and complement C3 levels over time.

level (Table 1). The Generalized Estimating Equations was used to determine the correlation between BMI and complement C3 levels over time. There was a statistically significant correlation between C3 and BMI changes.(%95 CI, 1.010 to 1.014 and p=0.02) (Fig. 1).

DISCUSSION

Levels of complement components varied with changes in body weight. As in other forms of starvation, complement levels were significantly decreased in low-weight anorectics even in the absence of complement activation by opportunistic infections and in protein deficiency which caused decreased serum complement levels (21). Our study provides that the decrease in complement C3 serum levels in AN patients increased with weight gain. These results support that body weight changes play a significant role in determining serum complement C3 levels.

Flierl et al. reported that complement consumption was secondary to increased activation in anorexic patients (29). Some authors have also suggested that the synthesis of C3 and transfer-rin in AN patients might be affected as a result of changes in the adipose tissue deposit (30). Adipose cells also synthesize other essential components of the alternative pathway, especially C3 and B (31). Pomeroy et al. (30) reported low serum complement levels due to hypoproduc-tion in AN. We concluded that both activation of the complement cascade by consumption and, alternatively, hypoproduction can be attributed to lower serum C3 levels in AN. However, there were no other consequences in the chronic activation of any disease or complement, such as any infection or malignancy, in patients throughout the study. Therefore, we thought that hypoproduction is the major cause of decreased complement C3 levels in AN in these patients.

There are few reports on complement levels in anorexia nervosa patients. Wyatt et. all published a series of five anorexia nervosa patients and observed significantly decreased serum levels of C1q, C2, C3, factor B, b luteinizing hormone (b-LH), C3b inactivator, properdin, and C4 bind-ing protein. After the initiation of alimentation, b-LH, C3b inactivator, C3, and factor B rapidly returned to the normal range in response to therapy (28). In line with these findings, Sigal et al. found low serum complement proteins levels in anorexia nervosa patients (32). A more recent report evaluated several components of the complement cascade and analyzed the activities of the alternative complement activation pathways (30). Serum levels of C3, Factor B and D, the hemolytic activity of the alternative pathway, and the inhibitors H and I were found to be low in anorexia patients and returned to normalwith weight gain (30). And recent studies have exam-ined complement hemolytic activation and complement hemolytic activity in anorexia nervosa patients and reported significantly lower serum C3 levels in AN compared to healthy controls, and a strong correlation between index C3 levels and BMI (29). In our study, we determined significantly decreased C3 complement levels in patients with anorexia nervosa, which is in line with previous findings. However, our study shows that C3 levels increase with weight restora-tion. Therefore, there may be complement C3 serum levels potentially

serving as a guide for monitoring the refeeding process.

As a result of general malnutrition, many laboratory anomalies are detected, while low C3 can be considered as a sign of low body weight. It is reasonable that serum C3 levels correlated with body weight in the anorexia group, reflecting the fact that a 'threshold' of severe illness caused by anorexia has been exceeded at these profoundly low body weights.

Low body weight and changes in body weight affect serum complement C3 levels. Low com-plement C3 levels were associated with increased risk of infection or other clinical pathologies with activation and consumption of complement cascade or were due to hypoproduction in adi-pose tissue or other sites of the body.

In our patients, not only low body weight, but also clinical features such as body image distor-tion and an intense fear of gaining weight decreased with increased C3 levels. Hence, C3 levels may represent treatment success to monitor.

Our study has a few limitations. Low patient numbers limit the power of our statistical analysis and make our data vulnerable to a statistical type II error. Therefore, our data do not allow ad-vocating complement serum levels as a marker for determining and monitoring the treatment until it is definitively proven in future large-scale prospective studies. And one of the limitations of our study is the absence of healthy control group.

In conclusion, our findings clearly demonstrate the role of body weight in determining levels of complement C3. C3 levels statistically correlated with weight restoration during treatment and thus C3 levels may be a useful marker for determining and monitoring treatment success in AN.

Contribution Categories		Author Initials
Category 1	Concept/Design	A.E.
	Data acquisition	A.E., M.O.
	Data analysis/Interpretation	A.E., M.O.
Category 2	Drafting manuscript	A.E., M.O.
	Critical revision of manuscript	A.E., M.O.
Category 3	Final approval and accountability	A.E., M.O.
Other	Technical or material support	A.E., M.O.
	Supervision	A.E.

Ethics Committee Approval: Study was approved by the Ethics Committee of Sakarya University Faculty of Medicine.

Informed Consent: During research the patient's oral and written informed consent was obtained from.

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