A Double Blind, Randomized Cross-Over Trial of Tyrosine Treatment on Cognitive Function and Psychological Parameters in Severe Hospitalized Anorexia Nervosa Patients

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ABSTRACT

Background: Anorexia nervosa (AN) is characterized by self-induced malnutrition, affecting body image, mood, cognition and survival. Tyrosine, an essential amino acid is the precursor of catecholamines. The use of tyrosine to treat AN is based on experiments on diet restricted mice, in which it increased food consumption, improved cognitive function and elevated brain catecholamines. We evaluated the effect of oral tyrosine administration on the cognition and emotional state of patients with AN. We hypothesized that tyrosine may improve cognitive function without changing body weight, thus “kick-start” nutritional rehabilitation.

Methods: 19 female hospitalized patients with chronic AN were supplemented with L-tyrosine (100 mg/kg/day)/placebo capsules for a three-week period in a double blind, randomized, cross-over study. Participants were evaluated cognitively and psychologically.

Results: Tyrosine shortened reaction time and test duration in memory tasks and improved depressive mood. No side effects were noted with the use of tyrosine.

Conclusions: Tyrosine may improve cognitive function and psychological traits associated with AN.

INTRODUCTION

Anorexia nervosa (AN) is a bio-psycho-social disorder in which changes in nutritional habits and body image distortion occur, leading to marked weight loss and malnutrition (1). Anorexia nervosa (AN) patients are characterized by perfectionism and obsessive personality traits. This AN-related personality type is associated with an exaggerated cognitive control and impaired cognitive-behavioral flexibility (2).

Essential amino acids including tyrosine, a precursor of catecholamines (CAs), are depleted in AN (3). Since lack of tyrosine may cause impaired cognition and distortion in body image, the patient sees himself as fat and continues dieting. These deficiencies may contribute to the physiologic-somatic and behavioral-psychologic changes, leading to a vicious cycle of dieting and weight loss (1).

Major weight loss and dieting can cause impairment in cognitive function even in healthy people (4). Studies on patients with AN have found a connection between lower body mass index and higher level of cognitive impairment, loss of short-time memory, reduced concentration and motor-perception ability, space-visual perception and problem-solving ability (4). Tyrosine transfer through the blood brain barrier (BBB) depends on other competing plasma amino acid concentrations and the nutritional status (5). The ratio of tyrosine to the other large neutral amino acids in starved animals is significantly lower than in controls. Administration of tyrosine to animals increases CA synthesis (6). Furthermore, tyrosine (100...
mg/kg/day orally) caused a 25% increase in CAs secretion during 24 hours relative to the basic normal level in healthy subjects (7). Tyrosine hydroxylase, the enzyme that synthesizes CAs, is usually unsaturated, and CA synthesis depends upon tyrosine availability (8). Tyrosine hydroxylase content and activity have been measured in various brain regions of AN patients and were shown to be markedly reduced in all brain regions. That may be as a result of low tyrosine levels (8).

We have previously shown in an animal-model of AN that tyrosine availability during severe diet restriction (DR) was a limiting factor in the synthesis and metabolism of norepinephrine. Severe DR in mice reduced cognitive function and adreno-receptor status that were restored by 100 mg/kg/day tyrosine administration. Further, the combination of DR and physical activity led to enhanced levels of serotonin. Administration of tyrosine normalized serotonin levels, improved food consumption, cognitive function and physical activity (less fatigue) (9).

CAs play a role in the patho-physiology of anxiety and mental disorders (10). Patients were classified as asymptomatic, improved or symptomatic. Affective and anxiety disorders were assessed by a structured psychiatric interview (Diagnostic Interview Schedule). In some cases of AN, when weight is restored, anxiety and depression disappear (10). Patients were classified as asymptomatic, improved or symptomatic. Affective and anxiety disorders were assessed by a structured psychiatric interview (Diagnostic Interview Schedule). Consequently, anxiety, depressive disorders and elevated stress seen in AN may result, in part, from a disturbance in CAs homeostasis caused by starvation (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11). Catecholaminergic neurotransmitters. In animals, administration of tyrosine, a food constituent and precursor of the catecholamines, reduces these behavioral and neurochemical deficits. Using a double-blind, placebo-controlled crossover design we investigated whether tyrosine (100 mg/kg) improved task performance, mood and cognitive function, and decreased diastolic blood pressure. Similarly, improvements in memory and psychomotor ability were observed (11).
The study parameters, including physical condition, were collected at three time points:

On admission (baseline), at the end of the first three-week period (first course) and at the end of the second three-week period (second course).

Participants were instructed to avoid driving, alcohol use, psychotropic drugs and drug abuse during the course of the experiment. They were requested to report any other drug used during the four weeks of experiment. A one-hour visit at the beginning of each week included score of weight gain, caloric consumption and psychiatric evaluation.

**STUDY MEASUREMENTS**

Neuropsychological indices: Neuropsychological parameters were collected using a computerized system, CTB-HPB (Computerized Test Battery for Assessment of Human Performance and Behavior, developed by the Israel Institute for Biological Research, Ness Ziona, Israel).

The following are five cognitive tests that were used and their theoretical constructs: Mark Numbers - Attention to Details and Quantitative Reasoning (14). Digit-symbol Substitution Test - Perceptual Speed and Associative Learning (a modified form of the Wechsler Test) (15). Successive Pattern Comparison - Spatial-visual Memory (16). Warrington Recognition Test - Verbal Memory (17). Four-Choice Serial Reaction Time - Psychomotor Ability (18).

In order to obtain reliable results, identical conditions were maintained in terms of test times, testing environment, presence and guidance of the same researcher, and random order of the tests.

Prior to testing, each patient was trained on the tests for seven sessions, thereafter performing the baseline test. Trainings were carried out before every test session throughout the study. This was done as training patients in neuropsychological tests can reduce anxiety and enhance cooperation.

**EMOTIONAL STATE AND TRAITS**

Psychiatric evaluation was performed at hospitalization as a semi-structured psychiatric interview in accordance with DSM-IV criteria and SCID-I questionnaire, Structural clinical interview for axis I (19). A senior psychiatrist carried out the psychiatric evaluation.

Psychological and behavioral traits data were evaluated by self-report questionnaires filled in at three points in time points mentioned above.

We used five questionnaires:

*Eating Disorders Inventory-2 (EDI-2)* (19). The EDI-2 is a widely used 91-item questionnaire designed to provide a broad assessment of the prevalence and intensity of psychological traits known to be associated with eating disorders. The EDI-2 is organized into 11 primary scales, three of which are specific to eating disorders and eight are general psychological scales that are highly relevant to eating disorders. It also provides six composites that measure eating disorder risk, ineffectiveness, interpersonal problems, affective problems, over-control, and general psychological maladjustment. The overall Summary Score was used as a primary outcome measure. The Hebrew translation of this inventory was found valid and reliable.

*Beck Depression Inventory (BDI)* (19) is one of the most widely used tools for assessing depressive symptoms in both clinical and non-clinical settings. It is a 21-item scale that asks responders to choose one out of four statements that best describes their feelings over the last two weeks. Responses are scored from 0-3, and total scores range from 0-63, with higher scores indicating greater levels of depressive symptomology. A score of 0-9 indicates no depression, 10-18 indicates mild depression, 19-29 indicates moderate depression and 30+ indicates severe depression.

*State-trait Anxiety Inventory (STAI)* (20) is a commonly used measure of trait and state anxiety. It is used in clinical settings to diagnose anxiety and to distinguish it from depressive syndromes. It also is often used in research as an indicator of caregiver distress.

*Multidimensional Perfectionism Scale (MPS)* (21). Perfectionism can lead to a variety of emotional, physical, and interpersonal problems. The MPS scale measures three trait dimensions of perfectionism — self-oriented, other-oriented, and socially prescribed — to help patients understand their behavior. The MPS explores the motivational, interpersonal, and cognitive aspects of perfectionistic behavior and relates those characteristics to mental and physical health problems, relationship problems and achievement difficulties.

*Leyton Obsessional Inventory*. The Leyton Obsessional Inventory (LOI) is a self-report questionnaire that assesses obsessional symptoms (22).

**ADDITIONAL NUTRITION SUPPLEMENTS**

Body weight was monitored weekly throughout the study. All patients received a well balanced diet with increased energy intake depending on weight gain, as well as vitamin D (200 IU) and calcium (400 mg) supplements. The patients received diet containing carbohydrates (55%), proteins (15-20%) and fatty acids (25-30%). Calorie intake elevated gradually. The increase in caloric intake
was about 500kcal per week from the initial intake of the patients (800kcal) in order to create 0.5kg increase in body weight until BMI reached the level of 19.

**MEDICATIONS**

Fifteen subjects of the study group (19) took psychiatric drugs during the study period. The most frequently used psychiatric drugs were from the SSRI group and risperidone (Risperdal). Some of these drugs can affect cognitive function. According to research evidence, this effect is not completely clear and it seems that if such an effect exists, it lasts a short time only (23).

**STATISTICAL ANALYSIS**

The effects of tyrosine/placebo on the dependent variables (neuropsychological and emotional parameters) compared to baseline were tested by MANOVA for repeated measures (SPSS version 17). If a significant difference was found in the F test, post hoc comparisons were carried out (using Bonferroni corrections, or simple main effects contrasts for interaction) to find out specific, significant differences. Data were tested for correlation (Pearson test) between BMI (with the same three points baseline, after tyrosine and after placebo) and the neuropsychological and emotional parameters.

**RESULTS**

**PARTICIPANTS**

The mean age of participants was 22.8 years (Table 1). Onset of disease was earlier, on average at the age of 16.5 years. The average duration of disease was 6.3 years. Many patients had suffered repeated episodes of the disease and were considered severe, chronic patients. Only two participants had not completed 12 years of schooling, whereas two participants had completed B.A. degrees.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study group (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>22.8 (5.4)</td>
</tr>
<tr>
<td>Onset of disease age (yrs)</td>
<td>16.5 (2.5)</td>
</tr>
<tr>
<td>Duration of disease yrs</td>
<td>6.3 (4.9)</td>
</tr>
<tr>
<td>Number of prior hospitalizations</td>
<td>1.4 (0.7)</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>12.6 (3.2)</td>
</tr>
<tr>
<td>Baseline BMI</td>
<td>15.5 (1.6)</td>
</tr>
<tr>
<td>BMI at the end of first course</td>
<td>17.4 (1.3)</td>
</tr>
<tr>
<td>BMI at the end of second course</td>
<td>18.9 (1.0)</td>
</tr>
</tbody>
</table>

*All values are mean ± SDs

**THE EFFECT ON BODY WEIGHT**

All the patients increased their body weight during the study although there was no significant change between the groups first treated with tyrosine or with placebo. It was a pre-exquisite that the patients had to gain weight or else they would have been withdrawn from the study.

**EFFECT OF TYROSINE ADMINISTRATION ON COGNITIVE FUNCTION**

There was no interaction between the order of treatment and changes in cognitive function. No correlation was observed between weight increase during the study and changes in cognitive function.

**WARRINGTON RECOGNITION TEST**

**Exam time:** Tyrosine administration resulted in a statistically significant shortening of the mean test time (p<0.05) as compared to baseline data, 383 sec. and 392 sec., respectively. Placebo administration also shortened mean exam time to 388 sec., but this result was not found to be of statistical significance (Figure 1).

**Response time:** The median response time for correct responses was shortened by both tyrosine (0.96 sec.) and placebo (0.91 sec.) administration, compared to baseline (1.04 sec.), in a statistically significant manner (p<0.001 for main effect) (Figure 2).

**MARK NUMBERS**

**Exam time:** The duration of this test was shortened compared to baseline for tyrosine administration, and this difference was close to statistical significance (p<0.067). A significant quadratic contrast (p<0.048) was found.

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**Figure 1. Effect of tyrosine treatment or placebo on time to complete the Warrington recognition exam in AN patients.**

Data are means ± SEM. There was a significant main effect of treatment (F(2/36)= 3.19, p<0.05). Post hoc, Bonferroni tests indicated that tyrosine treatment was significantly better than placebo (p<0.05). n=19
Tyrosine Treatment in Anorexia Nervosa

for tyrosine effect, indicating shortened exam time after tyrosine administration, whereas after placebo administration, exam time increased back to a level similar to baseline (Figure 3).

**Emotional state and traits:** We did not find any interaction between the order of treatment and emotional parameters. No correlation was observed between weight increase during the study and the emotional parameters.

**EFFECT OF TYROSINE ADMINISTRATION ON EMOTIONAL PARAMETERS**

Tyrosine administration resulted in a statistically significant reduced depression score compared to baseline (p<0.03). From mean BDI score of 26.9 at baseline, it reduced to 21.7 after tyrosine administration. After placebo administration the score was reduced to 23.3 (not significant), n=19 (Figure 4).

**EDI:** There was a significant decline in Drive for Thinness subscale, throughout the study by both tyrosine (M=9.4, SEM=1.6, F[1,18]=4.76, p=0.043) and placebo (M=9.3, SEM=1.7, F[1,17]=9.28, p=0.007), compared to baseline (M=12.0, SEM=1.6), n=19. The number presenting the reduction in the EDI-2 Drive for Thinness scale represents the median finding for both evaluation points.

In summary, tyrosine administration caused a statistically significant improvement in the parameters of test duration and shortened response times in the Warrington recognition test (verbal memory) and exam time of the Mark numbers test (attention to details and quantitative reasoning). In the Warrington recognition test response time was shortened by both tyrosine and placebo administration in a statistically significant manner.

Depression score was reduced significantly with tyrosine administration but not with placebo. No exclusive effect of tyrosine on EDI-2 was found. Other cognitive tests and the self-rating emotional scales were not different between the groups. There were no side effects except for the inconvenience of taking several capsules a day that were delivered during meals.

**DISCUSSION**

Anorexia nervosa is a multifactorial disorder (24) with bio-psycho-social antecedents. It is a chronic relapsing psychiatric disorder with a largely unknown pathophysiology. Dopamine has been implicated in the pathophysiology of

**Figure 4.** Effect of tyrosine treatment or placebo on Beck depression score in AN patients. Data are means ± SEM. There was a significant main effect of treatment (F[2/32]= 3.25, p<0.05). Post hoc, Bonferroni tests indicated that tyrosine treatment was significantly better than placebo (p<0.03). n=19
the disorder by both preclinical and clinical studies (25).

We postulated that part of the complex psychologically and emotional disturbances occur as a result of a lack of essential dietary-derived neurotransmitter precursors. We have focused on tyrosine and the catecholamine pathways since studies in animals and in human subjects suggest that its administration may affect brain CA levels and improve cognition and mood (25-27).

The present study investigated the effect of a single amino acid supplement on cognitive function and on emotional state of 19 hospitalized chronic AN patients. Most of them had been ill for more than five years before the study. This was as a randomized, double blind, crossover study. Each participant received a three-week course of 100 mg/kg tyrosine and a similar course of 100 mg/kg placebo per day.

Both the placebo and tyrosine groups were supplemented with similar amounts of proteins (1.5mg/kg) between 15-20% of the diet content as was indicated by the similar amount of blood albumin and globulin detected in their blood during the clinical trial.

In AN patients, when the body is under negative energy balance and elevated stress and characterized by decrease in proteins metabolism there is not enough tyrosine derived from the metabolism. Getting extra tyrosine by taking supplements may enhance its blood levels and availability, which increase its transfer through the BBB and might improve performance and memory as well as enhance body weight.

In order to obtain reliable results, we performed learning plots for all the patients in order to study the tests. Identical conditions were maintained regarding test times, testing environment, presence and guidance of the same researcher and random order of the tests.

Regarding cognitive function, the effect of tyrosine supplementation to AN patients was marked by increasing the rate and by hastening responses, as shown in the Warrington recognition test and Mark Numbers test. Apparently, memory-related performance is affected by tyrosine supplementation, as was found similarly in studies supplementing tyrosine to healthy subjects (12). Cerebral atrophy caused by AN is well described in the literature (28). We assumed that our participants may have had such changes as they suffered from chronic anorexia with many years of underweight and malnutrition. This may also be a reason that prevented them from achieving greater improvements. Weight, as an isolated factor, did not affect cognitive function or emotional parameters over the relatively short period of this study.

Emotional and behavioral assessments obtained from the self-administered questionnaires were of five types, examining the level of depression, the severity of the eating disorder, anxiety, perfectionism and the degree of obsessiveness. The reduction in depression score after tyrosine supplementation is compatible with evidence from previous studies (29). These studies showed favorable effect of tyrosine supplementation on depression both in patients and in healthy persons.

Tyrosine serves as a precursor of CAs, especially dopamine, which plays a central role in depression. In various studies, tyrosine supplementation was found to be associated with an improvement in depression levels, whereas in other studies, mood deterioration and dejection were observed in healthy persons supplemented with a tyrosine-free diet (29). Although we know from other studies that improvement in emotional parameters depends on weight and that there is a positive correlation between starvation and depression (30), with tyrosine supplementation we found an improvement in depression that was not connected to weight gain. Such an effect suggests that tyrosine might cause an improvement in mood before weight gain.

The Drive for Thinness sub-scale derived from EDI-1 improved significantly by both tyrosine and placebo. This is an encouraging finding since we know from prospective studies that changes in attitudes may take longer time, even a few years after maintaining normal weight and menses, as shown in the treatment of abnormal attitudes and traits (31).

Limitations of the study include the fact that it was undertaken in hospitalized patients with severe AN. This precludes the generalization of the findings to ambulatory populations with less severe illness. As in other studies, we also encountered a few cases of placebo effect. One can explain this by the contribution of a more personalized relationship with the test subjects, by the increased attention paid to them deriving from the study.

We found large variance in cognitive results which reduced the statistical significance. We are aware of the fact that most of the test subjects (15 patients) were undergoing an intensive treatment process, and received in some phase of the study psychiatric drugs that were liable to influence cognitive function. Also, the limited number of participants included chronic patients in serious condition who may experience some irreversible brain changes and are not the most suitable candidates for such treatment. In addition diagnosis was achieved
only by one evaluator. We have not assessed the validity (Cronbach Alpha) of the self-rating scales for the present study.

Results might be more favorable in patients with AN at the onset of their disease, especially since the treatment is without side effects. There is a need for future studies that should be carried out on a large scale. The effect of tyrosine administration can be tested over a longer time period and, also, in a larger dosage of 150 mg/kg (as already documented in the literature), where it is possible that the effect might be greater. Tyrosine should also be tested in patients with early disease. Chronic patients should be tested separately from non-chronic patients, thus reducing the variance in the cognitive findings.

In summary, tyrosine supplementation has a beneficial effect on cognitive function and depression in patients with severe chronic anorexia nervosa. Tyrosine supplementation might prove to be a useful treatment in the management of patients with anorexia nervosa.

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Author Disclosure
No conflict of Interest

References


