# Oral Tyrosine Supplementation Facilitates Conditions for the Preferential Transport of Tyrosine Across the Blood-Brain Barrier in Anorexia Nervosa: a Case Study Series

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# Abstract

***Background***: Anorexia nervosa is a severe and complex illness associated with a lack of efficacious treatment. Ongoing tyrosine administration has been proposed as a possible treatment through increasing blood tyrosine sufficiently to facilitate brain catecholamine synthesis. Saturation with the noradrenergic precursor tyrosine could alleviate noradrenergic dysregulation with subsequent reduction in dietary restraint and eating, weight and shape concern. The effects of tyrosine supplementation in adolescents with anorexia nervosa remain to be tested. This feasibility study aimed to explore whether an oral tyrosine dosage raises plasma tyrosine sufficiently in adolescents with anorexia nervosa and healthy peers and is sustained over time to allow conditions for the preferential transport across the blood-brain barrier.

***Case Presentation***: The first stage of this study explored the pharmacological response to a single, oral tyrosine load in adolescents (aged 12-15 years) with anorexia nervosa (*n*=2) and healthy peers (*n*=2). The second stage explored the pharmacological and psychological response to ongoing tyrosine administration in adolescents with anorexia nervosa. Peak tyrosine levels occurred at approximately two-three hours and approached baseline levels by eight hours. Blood tyrosine elevation was maintained over time in participants with anorexia nervosa. Some improvements in participant psychological tests were evident. There were no measured side effects.

***Conclusions***: The considerable blood tyrosine increase appeared sufficient to facilitate conditions for the preferential transport of tyrosine across the blood-brain barrier which has the potential to improve noradrenergic brain function in people with anorexia nervosa. Further exploration of tyrosine as an adjunct treatment in anorexia nervosa is warranted.


# Background

Anorexia nervosa (AN) is a severe and complex illness with high mortality, poorly understood pathophysiology and lack of efficacious treatments (1). Weight or shape preoccupation, extreme measures to lose weight, low body weight and excessive self-evaluation of weight and shape are key characteristics (2). Lifetime prevalence of AN has been estimated at 0.3%-4.3% and incidence of eating disorders appears highest in the 15-19 year age group (3, 4). There is a pressing need for interventions to modify causal and maintaining factors in AN. Noradrenaline is an important neurotransmitter in the self-regulatory system of the brain (5). Brain noradrenergic dysregulation has been posited as a key causative factor, contributing to body image disturbance and dietary restraint (6). Hart and colleagues (2013) have furthered this model, hypothesizing that ongoing administration of tyrosine may alleviate some of the pathological changes found in AN (7). Saturation of supply of the noradrenergic precursor tyrosine could alleviate noradrenergic dysregulation with subsequent reduction in dietary restraint and concern for eating, weight and shape (7). This hypothesis relies on increasing blood tyrosine sufficiently to facilitate brain catecholamine synthesis.

Tyrosine, the precursor to the catecholamines dopamine, noradrenaline and adrenaline, is considered a “conditionally-indispensable” dietary amino acid, with synthesis dependent upon the availability of phenylalanine (8, 9). Tyrosine is one of the large, neutral amino acids and is derived directly from dietary intake, hydrolysis of tissue proteins or hydroxylation of phenylalanine. Severe starvation (as occurs in AN) tends to depress circulating levels of the essential amino acids, with tyrosine particularly depressed (10). Ingestion of tyrosine has been found to increase plasma tyrosine levels, elevate brain tyrosine and may increase the synthesis of dopamine and noradrenaline (11-13). Tyrosine supplementation may prove a useful adjunct to treatment in AN, provided blood tyrosine levels are sufficiently elevated to facilitate brain catecholamine synthesis. This case study series aimed to explore whether the manufactured tyrosine dosage produced an adequate rise in plasma tyrosine and to test study procedures or potential problems associated with tyrosine administration in a small sample of adolescents with AN and healthy peers.

## Case Presentation

In the first stage of the study, the response to a single 2.5g oral L-tyrosine load in two female adolescents with AN and two healthy peers, while on a low protein, low biogenic amine diet was tested. The second stage of the study involved tyrosine administration at 2.5g twice daily for a 12 week period in participants with AN. Testing occurred at baseline and at weeks one, six and 12. The study had approval from the health service and the University Human Research Ethics Committees. Participants and their parent provided signed informed consent.

*Recruitment*

Healthy female volunteers aged 12-17 years residing in New South Wales, Australia, were recruited through posters in a tertiary hospital and local community health centers from October to December 2006. Exclusion criteria included known significant medical or psychiatric illness, drug or alcohol abuse in the past six months, use of any amino acid supplement within past three months or current use of psychiatric medications. Healthy participants were screened for eligibility, including completion of psychological testing to exclude psychiatric illness. Height and weight measures were taken to ensure participants were not outside the acceptable body mass index (BMI) range based on BMI-for-Age Percentile Charts (14).

Criteria for participants with AN included 12-17 year old females admitted with AN to a tertiary hospital specialist child and adolescent mental health ward or pediatric ward in Newcastle, New South Wales, Australia. Diagnosis was confirmed by the Eating Disorders Examination (EDE) interview (child version), administered by a trained clinician (15). Exclusion criteria included use of any amino acid supplement within the previous three months, medical instability, concurrent severe medical or neurological illness, Phenylketonuria or drug or alcohol abuse within the previous six months. Participants requiring noradrenergic or combined noradrenergic medications or stimulant medication were excluded. Recruitment of participants with AN occurred from February 2007 to March 2010.

*Intervention factors*

All participants followed a low protein, low biogenic amine diet for the day prior to and initial day of testing, and fasted from 10pm the day prior to testing, until after the initial collection of study blood and urine (eight hours). Dietary protein intake was strictly limited to ≤7g per main meal and ≤1g per mid-meal on the day prior to testing and to ≤2.5g per main meal and ≤1g per mid-meal on the day of testing. Instructions in how to limit protein and amino acids and exclude foods known to be vasoactive or to influence urinary catecholamines or their metabolites (16, 17) were provided to participants and their parent by an experienced clinical dietitian. Parents supervised and supplied food for the diet for healthy participants. Healthy participants were required to keep a strict food and fluid diary during the special diet period (two days). For participants with AN, the diet was prepared, meals were supervised and a strict food and fluid diary was kept by inpatient pediatric nursing staff.

Tyrosine requirements for an average-weight female adolescent are estimated to be 1750-2050mg/day (18), with no observed side effects for intakes as high as 100-500mg/kg tyrosine in adults (19-23). Supplemental amounts of 100-300mg/kg have shown functional improvements in humans such as improved cognitive function (23-25). The tyrosine dosage deemed to be of clinical benefit for this study was therefore set at 100mg/kg/day expected body weight. Based on the average expected weight for a female adolescent (approximately 50kg) (14), the standard daily dose was set at 5g/day. Due to the short half-life of tyrosine (peak two-three hours post-ingestion) (19-21, 26) tyrosine was delivered as a split dose, at two 2.5g doses per day (morning and evening), administered orally in capsulated form.

Participants in the first stage of this study were required to ingest a single 2.5g tyrosine load after an overnight fast. Participants were reviewed by the hospital pediatrician four hours after tyrosine administration and monitored by

nursing staff for eight hours after administering the initial tyrosine load. Participants with AN ingested twice daily 2.5g tyrosine doses for 12 weeks at pre-determined times (approximately 12 hours apart) at least 30 minutes before or one hour after meals to assist with absorption. The tyrosine was taken with a minimum of 100mls of fluid, preferably orange juice, as ascorbic acid is required as a cofactor in noradrenaline synthesis (27). Nursing staff administered supplements during hospital admissions, and parents supervised administration at home. Participants with AN were monitored in hospital by nursing and medical staff for the first four days of tyrosine supplementation. Participants were contacted fortnightly by the researcher to monitor compliance with the supplement regime. Supplements were provided by pharmacy twice throughout the study and unused supplements collected.

As phenylalanine is converted to tyrosine, dietary intake of tyrosine and phenylalanine in participants with AN were estimated using 24-hour recalls collected at four time points to coincide with blood and urine testing (28). To minimise respondent bias, participants were informed that they would be contacted four times throughout the study for dietary recalls and that the timing of recalls would not be disclosed in advance. A trained clinical dietitian administered the recalls using visual aides (plate, cup and ruler) and analysed data using a nutritional analysis program (29). Dietary sources high in protein, amino acids and aspartame (artificial sweetener), known to be high in people with an eating disorder and to influence plasma phenylalanine (30), were emphasised during collections.

*Outcome measures*

Blood tyrosine level was the main outcome measure. For the first stage of the study, blood samples were taken four hours prior to tyrosine ingestion (fasting), immediately prior to tyrosine administration and at 1, 2, 3, 4, 6 and 8 hours after supplement ingestion. Blood samples for the second stage of the study were taken at baseline (immediately prior to supplement administration) and two hours later at weeks one, six and 12 in participants with AN, allowing for estimation of trough and peak blood tyrosine levels. In those with AN, blood spot samples (whole blood dried on filter paper) were taken at every blood collection for quality monitoring purposes.

For healthy peers, heparinized plasma samples were analyzed by an independent National Association of Testing Authorities (NATA)-accredited laboratory using high performance liquid chromatography (HPLC) with electrochemical detection. Due to resource issues within the laboratory, plasma samples were unable to be analyzed for participants with AN at completion of this study and only blood spot analyses were used. Blood spot samples were analyzed at a NATA-accredited laboratory using electrospray tandem mass spectrometry in dried-blood-spots with underivatised samples (31). Within the laboratory, tyrosine levels in dried blood spots measured by tandem mass spectrometry and those in plasma, taken from the same blood samples and measured by ion-exchange chromatography, correlated well.

For the first stage of the study, urine samples were conducted as timed collections four hours before supplement ingestion (fasting sample), at baseline (supplement ingestion), then at four and eight hours after tyrosine administration. For the second stage, urine samples were collected 4 hours post-supplementation at weeks one, six and 12. Samples were analyzed by an independent NATA-accredited laboratory using HPLC with electrochemical detection adapted from Riggen and Kissinger (32). Urinary tyrosine and catecholamine activity was measured, including tyrosine, dopamine, noradrenaline, adrenaline, homovanillic acid, vanillylmandelic acid and 5-hydroxyindoleacetic acid.

Height and weight measurements were taken by pediatric nursing staff using the same calibrated digital scales and a stadiometer. Weight was measured to the nearest 0.1kg and height to the nearest 0.5cm, without shoes or heavy clothing. In participants with AN, height and weight were taken at baseline, six weeks and 12 weeks. Percent expected body weight calculations were based on the Centre for Disease Control Body Mass Index (BMI) Percentile Charts (14), with 100% weight for height being the 50th percentile BMI.

Participants and their parent or carer each completed a brief purpose-developed questionnaire in pencil and paper format regarding perceived study acceptability. To assess the possible effects of tyrosine administration and catecholamine synthesis in the brain, a range of psychological tests were administered to participants with AN. To measure eating disorders psychopathology, the EDE was administered at baseline and week 12 (15). Anxiety was measured at baseline and weeks one, six and 12 using the State-Trait Anxiety Inventory Form Y-1 (33). Depressive and obsessive compulsive symptoms were measured at baseline and weeks six and 12 using the Children's Depression Inventory (34) and the Children's Obsessive Compulsive Inventory (35) respectively. The Strengths and Difficulties Questionnaire was administered at baseline and weeks six and 12 as a general mental health measure (36).

A standardised battery of cognitive function tests were administered by experienced clinical psychologists at baseline and week 12. These were: Rey Complex Figure Test (Meyer and Meyer) initially copy and 30 minute recall (37), Verbal Fluency (FAS) Condition One (Baron) (38), Tower Task (Krikorian) (39), Stroop Color-Word task (Golden) (40), Verbal Paired Associate Learning (Wechsler Memory Scale, Revised) (41), Digit Symbol-Coding (Wechsler Intelligence Scale for Children, Fourth Edition) (42), Visual Learning (Wide Range Assessment of Memory and Learning) (43), Matching (Wide Range Assessment of Visual-Motor Abilities) (44), Trail Making (Reitan) (45) and Design Fluency (46). The Wide Range Achievement Test-3 Reading Test (47) was used as a measure of executive function. An experienced neuropsychologist converted participant test scores to normative data and applied ability ranges. In order to minimise systematic error (e.g. practice effects) or measurement error (e.g. test unreliability) in psychological tests, reliable change index (RCI) methods were used to examine change in psychological tests (48).

### Participants and characteristics

Healthy peers were both female, aged 14 years and had a percentage expected body weight of 100-110%. Participant 1 with AN was 15 years of age, weighed 46kg at baseline and had been amenorrheic for three months. Participant 2 was 12 years of age, weighed 37kg at baseline and remained pre-menarchal. Both AN participants had a relatively short duration of illness (three months) and similar expected body weights at baseline (80-82%). Neither participant with AN had received treatment prior to the recent hospital admission and had no comorbid medical or psychiatric diagnoses. Both participants with AN were taking multivitamin, thiamine and phosphate supplements at baseline, though no other medications. Both participants were refed on the pediatric ward for the initial 2 weeks of the study, then attended CAMHS for weekly family therapy interventions. Participant 1 with AN had a secondary diagnosis of obsessive compulsive disorder at completion of the study. Both participants had consumed Olanzapine (an antipsychotic) at times during the study and Participant 1 also consumed Lorazepam (a benzodiazepine) towards the end of the study. Participant 1 reported several self-induced vomiting episodes before and during the study, though denied other purgative behavior. Binge eating and excessive exercise behavior were denied by both participants.

### Dosage and dietary intakes

The initial 2.5g tyrosine load equated to a dosage of 45-47mg/kg actual body weight in the healthy participants. The dosage for Participant 1 with AN was 54mg/kg and for Participant 2 68mg/kg. Dietary intakes for all participants in the first stage remained within required protein restrictions for the day before and day of testing. With the ongoing 5g daily tyrosine dose for the participants with AN, Participant 1 received a slightly smaller average dose of tyrosine (110mg/kg/day) and had lower average dietary intakes (protein 55g, tyrosine 2.2g and phenylalanine 2.4g), though fewer unused supplements (<1%). The average tyrosine dose for Participant 2 was 121mg/kg/day with average daily dietary intakes of 94g protein, 3.8g tyrosine and 4.1g phenylalanine.

### Outcome for blood, urine and expected body weight

On day one, baseline (time 0) plasma tyrosine concentrations were similar for all four participants (48-60μmol/L) (Figure 1). Peak tyrosine levels were observed at approximately two-three hours (132-240μmol/L) and approached baseline levels by eight hours (62-100μmol/L). Percentage change in plasma tyrosine (between trough and peak levels) ranged from 152-194% in healthy peers and 164-300% in participants with AN. Participant 1 with AN had a notably higher peak tyrosine response, nearly double that of other participants. Urinary tyrosine concentrations were too low for reliable quantification by the method used for all participants at all time points. There were no consistent changes over time in urinary catecholamines or metabolites, and no values exceeded the normal reference range.

By the end of stage two, percent expected body weight remained essentially unchanged (80%) in Participant 1, while Participant 2 was relatively weight-restored (96%). Table 1 details the blood tyrosine response to an oral tyrosine load in participants over 12 weeks. There was a chronic rise in blood tyrosine during the course of the study, and an acute rise two hours after supplement administration. In Participant 2, the morning trough level normalized by week 12. In Participant 1 this did not occur, though the magnitude of the acute rise diminished.

### Psychological tests and side effects

Some improvements in participant psychological tests were evident, with no notable declines. While both participants remained within the clinically significant range for eating disorders psychopathology over the 12 weeks (Table 2), there was a statistically significant improvement in Eating Restraint (RCI=-2.50) and the Global Score (RCI=-1.65) for Participant 2. Non-significant improvements in both Weight and Shape Concern were found in both participants, along with a non-significant increase in Eating Concern. Clinically significant improvements in Trait Anxiety (Table 3) and depression scores for Anhedonia were found for both participants, and in Participant 2 for the depressive symptoms Total Score, Negative Mood, Ineffectiveness and Negative Self-Esteem (Table 4). For Participant 1, there were clinically significant increases in Interpersonal Problems and Ineffectiveness. For obsessive compulsive symptomology, improvements were evident in most symptom subscales and Total Impairment, aside from Obsessions Severity which increased in Participant 1. Total Impairment remained in the clinically significant range, aside from moving temporarily into the normal range at week six in Participant 2.

Clinically significant neurocognitive improvements were observed in both participants for the Tower of London task and for the Trail Making B task in Participant 1. A clinically and statistically significant decline (from Very Superior to Superior ability range) in Participant 2 for Digit Symbol Coding was evident. There were no consistent trends in most general mental health scales. For Participant 1, clinically significant increases in Emotional Problems, Peer Problems and Total Difficulties were found.

No side effects associated with tyrosine administration were observed or reported by participants, nursing staff or the pediatrician. Participant 1 was admitted to a child and adolescent mental health ward ten-and-a-half weeks after commencing supplementation. No decline was evident by week 12 in the total scores for eating disorders psychopathology, anxiety, depression or obsessive compulsive symptoms, and there was no notable decline in cognitive performance. Some increase was evident in Total Difficulties on the general mental health measure for Participant 1.

## Discussion And Conclusions

This study offered an in-depth exploration of the effects of tyrosine supplementation in adolescents with AN and healthy peers. The ongoing 5g daily dosage of tyrosine resulted in a chronic rise in blood tyrosine in participants with AN, which may allow for brain substrate repletion. It is assumed that the considerable increase in blood tyrosine facilitated conditions for the preferential transport of tyrosine across the blood-brain barrier. By week 12, the morning trough blood tyrosine level had normalised in one participant and the magnitude of the response to tyrosine dosage

diminished in the other. This could suggest up-regulation at different points in the metabolic pathway, consistent with the hypothesis proposed by Hart et al (2013) (7). The maintained rise in blood tyrosine, suggests that tyrosine availability in the brain could have been maintained over the study period, allowing substrate repletion with positive effects on behavioural aspects of the illness. Improvements (particularly in Participant 2) in eating disorder psychopathology, anxiety, depressive and obsessive compulsive symptoms and in some executive function tests were found.

Tyrosine appeared to be well absorbed, despite its fairly insoluble nature (49). Consistent with a previous study of adults, peak tyrosine concentrations occurred approximately two to three hours post-supplement administration and approached baseline levels by eight hours (19). A 30%-50% increase in plasma tyrosine has been suggested to be sufficient to produce changes in brain tyrosine concentrations in rats (50, 51). All participants exceeded this increase in plasma/blood tyrosine following tyrosine administration. Increases were similar to those found in one study of healthy males (153% increase) (21), although were more pronounced than a two-fold increase reported in another study of adults with mild hypertension (20). This second study, however, tested participants after 14 days of supplementation, which may have resulted in some biological adaption. The exogenous effects of food intake could also contribute to differences in tyrosine concentrations seen in different studies. One participant with AN had a notably higher peak tyrosine response, which could be due to metabolic variation. Dosage does not appear to account for this increase as the participant had a lower tyrosine dosage per kg body weight than the other participant with AN.

Despite some evidence suggesting that blood tyrosine levels may be lowered in severe dietary restriction (52) and in the starvation phase of AN (52-54), this was not observed in the baseline results for the participants with AN. Fasting blood tyrosine levels (pre-loading) were similar in participants with AN and healthy peers. This may have been influenced by participants with AN being actively re-fed during their inpatient treatment prior to baseline measures.

Urinary catecholamine or metabolite excretion did not appear to change in response to tyrosine administration. Monoamine renal physiology appears complex and it has recently been argued that (aside from screening for tumors that secrete serotonin, noradrenaline and dopamine) interpretation of spot urine catecholamines and metabolites holds little value (55). This may be explained by the complex renal physiologic interactions between amino acids newly synthesized in the kidneys, and the fact that some monoamines are filtered at the glomerulus and metabolized in the kidneys, with no significant amount eliminated in urine (55, 56). As such, removal of urinary measures in future studies of tyrosine administration should be considered.

One participant was admitted to a mental health ward ten-and-a-half weeks after commencing supplementation. Deterioration in eating disorders psychopathology, anxiety, depression or obsessive compulsive symptoms was not evident. This participant had a lower average tyrosine dosage compared to the other participant and lower average dietary intakes of energy, protein, tyrosine and phenylalanine. Higher estimated trough and peak blood tyrosine levels were found in this participant.

There are several limitations which require consideration. The use of psychiatric medications and nutritional supplements could not be controlled for in participants with AN. Olanzapine has a small secondary effect on noradrenaline because of its dopamine and alpha adrenergic blockade, while Lorazepam is a primarily gamma aminobutyric acid modulator and has effects on the adrenergic system as an indirect inhibitor (57). However, neither are known to effect bioavailability, metabolism or elimination of tyrosine (57). The percentage ideal body weight of participants differed at week 12, suggesting marked differences in nutritional status. Ascorbate and thiamine ingestion may have varied and assisted tyrosine metabolism by ensuring co-factor availability. Similarly, phosphate assists essential phosphorylation of second messenger systems and variation in phosphate intake may have occurred.

Variable compliance with tyrosine administration is also a possibility. Self-induced vomiting was reported in one participant, and could affect tyrosine absorption if this occurred shortly after tyrosine administration.

This case study series contributes to the very limited knowledge base regarding normative pharmacokinetics of tyrosine loading in AN. The results of this study suggest that a 2.5g oral dose of tyrosine in adolescents with AN and healthy peers is adequately absorbed and produces a rise in blood tyrosine concentration that may facilitate preferential transfer across the blood-brain barrier. The maintained rise in blood tyrosine over time could allow for substrate repletion in AN. Variation in blood and psychological response to tyrosine administration were observed and further exploration in a larger sample is warranted, including exploring the effects of age, medications and nutritional and psychological status on tyrosine response.

## Abbreviations

AN: anorexia nervosa; BMI: body mass index; EDE (Eating Disorders Examination; NATA: National Association of Testing Authorities; HPLC: high performance liquid chromatography.

## Declarations

**Ethics Approval and Consent to Participate:** this study had approval from the Hunter New England Human Research Ethics Committee and the University of Newcastle Human Research Ethics. Participants and their parent/carer provided signed informed consent prior to participating in the study.

**Consent for Publication:** Not all participant details were included in the manuscript to prevent identification. Data being included in publications and reports was described in the Information Statement, which participants provided written consented to.

**Availability of Data and Materials:** The datasets generated and/or analysed during the current study are not publicly available due to participant privacy reasons, but are available from the corresponding author on reasonable request.

**Competing Interests:** The authors declare that they have no competing interests.

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**Author Contributions:** MH completed the study as part of her PhD, contributed to the design, developed research protocols, conducted the study and prepared and revised the manuscript. DS contributed to the study conception, design, methodology and analysis. LW provided guidance around study implementation and provided significant contribution to manuscript review. KN contributed to the study concept, design and implementation. BW contributed to the study design, development of protocols and implementation. All authors read and approved the final manuscript.

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# Tables

**Table 1. Blood Tyrosine Response to Oral Tyrosine Load in Participants with Anorexia Nervosa Over Twelve weeks (*n*=2) (µmol/L)**

| Time Point (μmol/L) | Time 1 (0 Hours, Estimated Trough) | Time 2 (2 Hours, Estimated Peak) | Absolute Difference (% Change) |
|---|---|---|---|
| Baseline | | | |
| Participant 1 | 60 | 190† | 130 (217%) |
| Participant 2 | 59 | 156† | 97 (164%) |
| Week 1 | | | |
| Participant 1 | 140† | 390† | 250 (179%) |
| Participant 2 | 125† | 372† | 247 (198%) |
| Week 6 | | | |
| Participant 1 | 140† | 290† | 150 (107%) |
| Participant 2 | 91 | 278† | 187 (205%) |
| Week 12 | | | |
| Participant 1 | 230† | 340† | 110 (48%) |
| Participant 2 | 50 | 161† | 111 (222%) |

Note: Time 1 denotes the time of supplement administration and Time 2 denotes two hours post-tyrosine administration. † denotes outside the reference range.

**Table 2. Change in Participant Eating Disorders Psychopathology Following Twelve Weeks of Tyrosine Supplementation (*n*=2)**

| Eating Disorders Examination (Child Version) Scales | Baseline | Week 12 | Absolute Difference (% Change) | RCI |
|---|---|---|---|---|
| **Participant 1** | | | | |
| Restraint | 6.0† | 6.0† | 0 (0%) | 0.00 |
| Eating Concern | 3.4† | 4.6† | 1.2 (35%) | 1.63 |
| Weight Concern | 5.2† | 4.6† | -0.6 (-12%) | -0.76 |
| Shape Concern | 4.9† | 3.8† | -1.13 (-23%) | -1.39 |
| Global Score | 4.9† | 4.7† | -0.13 (-3%) | -0.37 |
| **Participant 2** | | | | |
| Restraint | 5.0† | 2.2† | -2.8 (-56%) | -2.50* |
| Eating Concern | 3.4† | 4.2† | 0.8 (24%) | 1.09 |
| Weight Concern | 5.2† | 4.6† | -0.6 (-12%) | -0.76 |
| Shape Concern | 5.9† | 4.9† | -1.0 (-17%) | -1.26 |
| Global Score | 4.9† | 4.0† | -0.9 (-18%) | -1.65* |

Note: Absolute Difference denotes the difference in participant baseline and follow up scores; % Change denotes percentage change in participant raw scores over time; RCI denotes Reliable Change Index (Jacobson et al, 1991); † denotes within the clinically significant range, based on a z score of two or more (calculated from Wade et al, 2008); and * denotes a significant reliable change over time (Duff, 2012).

**Table 3: Change in Participant State and Trait Anxiety Following Twelve Weeks of Tyrosine Administration (*n*=2)**

| | Baseline | Week 1 | | Week 6 | | Week 12 | |
|---|---|---|---|---|---|---|---|
| Anxiety Scale | Raw Score (Std Score) [Percentile] | Raw Score (Std Score) [Percentile] | Absolute Difference (% Change) | Raw Score (Std Score) [Percentile] | Absolute Difference (% Change) | Raw Score (Std Score) [Percentile] | Absolute Difference (% Change) |
| **Participant 1** | | | | | | | |
| State Anxiety | 59 (64) [92] | 57 (63) [89] | -2 (-3%) | 42 (51) [58] | -17 (-29%) | 51 (58) [82] | -8 (-14%) |
| Trait Anxiety | 66 (74) [98] † | 50 (59) [80] ‡ | -16 (-24%) | 59 (67) [95] | -7 (-11%) | 57 (65) [89] | -9 (-14%) |
| **Participant 2** | | | | | | | |
| State Anxiety | 53 (60) [86] | 57 (63) [89] | 4 (8%) | 58 (64) [90] | 5 (9%) | 52 (59) [84] | -1 (-2%) |
| Trait Anxiety | 71 (78) [99] † | 65 (73) [98] † | -6 (-8%) | 55 (63) [91] ‡ | -16 (-23%) | 48 (57) [76] | -23 (-32%) |

Note: Std Score denotes standard score; % Change denotes percentage change in raw score over time; † denotes clinically significant anxiety symptoms based on 2 or more standard deviations from the mean (T score of 70 or more) (Dancey, 2008; Gregory, 2011); and ‡ denotes a clinically significant change (moved into or out of the clinically significant range).

**Table 4: Change in Participant Depressive Symptomatology Over Twelve Weeks of Tyrosine Administration (*n*=2)**

| | Baseline | | Week 6 | | | Week 12 | | |
|---|---|---|---|---|---|---|---|---|
| Symptom Scale | Raw Score (T Score) | Interpretive Guideline | Raw Score (T Score) | Interpretive Guideline | Absolute Difference (% Change) | Raw Score (T Score) | Interpretive Guideline | Absolute Difference (% Change) |
| Negative Mood | | | | | | | | |
| Participant 1 | 7 (75) † | Very Much Above Average | 5 (64) ‡ | Above Average | -2 (-29%) | 6 (70) †‡ | Very Much Above Average | -1 (-14%) |
| Participant 2 | 8 (81) † | Very Much Above Average | 9 (86) † | Very Much Above Average | 1 (13%) | 3 (54) ‡ | Average | -5 (-63%) |
| Interpersonal Problems | | | | | | | | |
| Participant 1 | 2 (64) | Above Average | 3 (74) †‡ | Very Much Above Average | 1 (50%) | 4 (84) † | Very Much Above Average | 2 (100%) |
| Participant 2 | 1 (54) | Average | 0 (43) | Slightly Below Average | -1 (-100%) | 1 (54) | Average | 0 (0%) |
| Ineffectiveness | | | | | | | | |
| Participant 1 | 2 (52) | Average | 2 (52) | Average | 0 (0%) | 4 (66) †‡ | Very Much Above Average | 2 (100%) |
| Participant 2 | 5 (74) † | Very Much Above Average | 5 (74) † | Very Much Above Average | 0 (0%) | 2 (52) ‡ | Average | -3 (-60%) |
| Anhedonia | | | | | | | | |
| Participant 1 | 12 (82) † | Very Much Above Average | 7 (63) ‡ | Above Average | -5 (-42%) | 7 (63) | Above Average | -5 (-42%) |
| Participant 2 | 12 (82) † | Very Much Above Average | 5 (56) ‡ | Slightly Above Average | -7 (-58%) | 3 (49) | Average | -9 (-75%) |
| Negative Self-Esteem | | | | | | | | |
| Participant 1 | 4 (64) | Above Average | 4 (64) | Above Average | 0 (0%) | 4 (64) | Above Average | 0 (0%) |
| Participant 2 | 5 (70) † | Very Much Above Average | 4 (64) ‡ | Above Average | -1 (-20%) | 3 (58) | Slightly Above Average | -2 (-40%) |
| Total Score | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Participant 1 | 27 (78) † | Very Much Above Average | 21 (68) † | Very Much Above Average | -6 (-22%) | 25 (74) † | Very Much Above Average | -2 (-7%) |
| Participant 2 | 31 (84) † | Very Much Above Average | 23 (71) † | Very Much Above Average | -8 (-26%) | 12 (54) ‡ | Average | -19 (-61%) |

Note: Absolute Difference denotes the difference in participant baseline and follow-up raw scores; % Change denotes percentage change in raw score from baseline; † denotes clinically significant depressive symptomatology, based on guidelines from Kovacs (1992); and ‡ denotes a clinically significant change (moved into or out of the clinically significant range).

## Figures

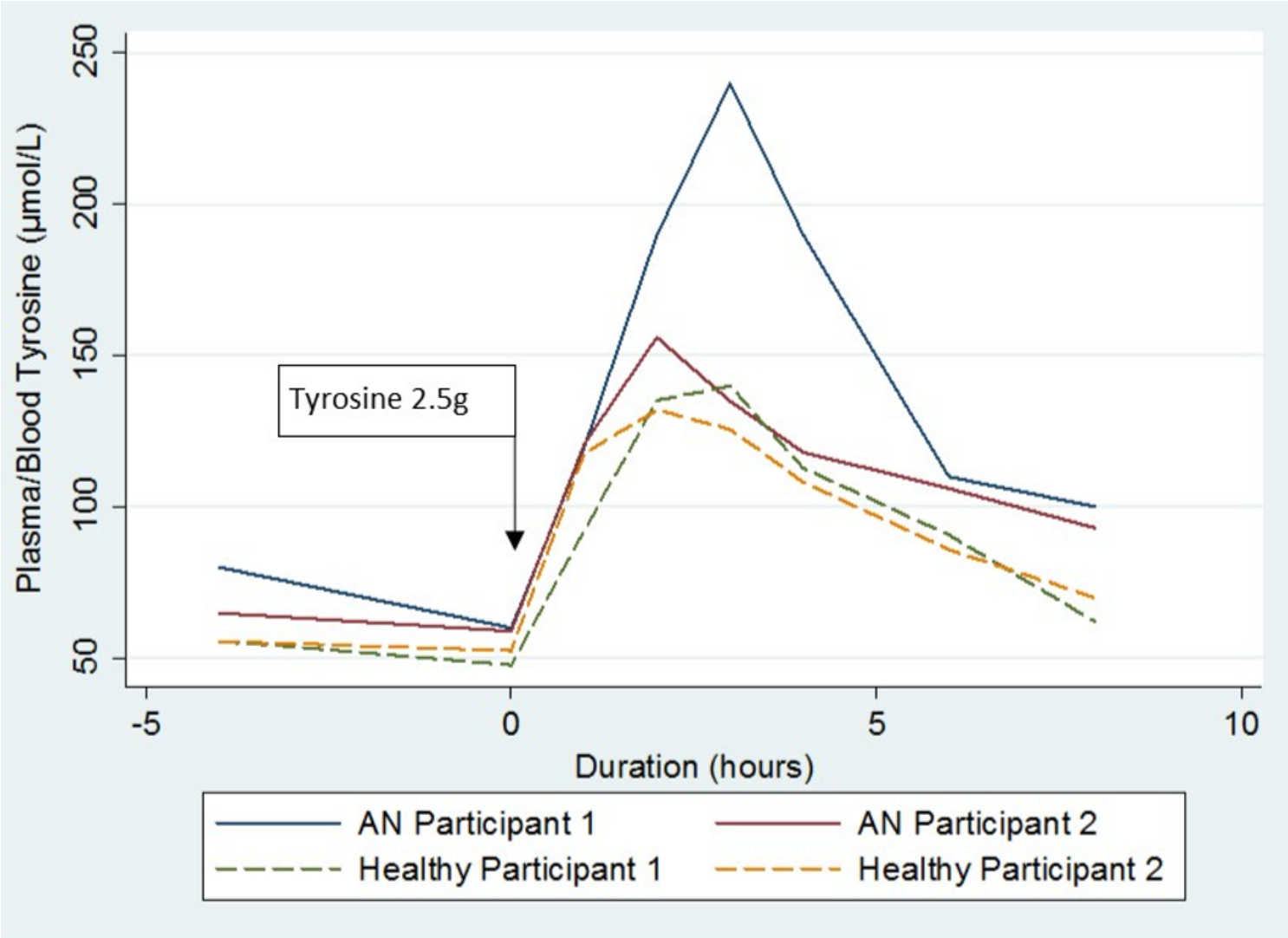


**Figure 1**

Blood Tyrosine in Anorexia Nervosa (n=2) and Control Plasma Tyrosine (n=2) Response to Tyrosine Load

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CAREchecklistMHart16.2.21.pdf