

## 学位論文要約

論文題目 The characteristics of young adults with subclinical depression and the beneficial effect of tryptophan, vitamin B<sub>6</sub>, and nicotinamide-containing supplement loading between meals on their depressive mood

(抑うつ傾向の若年成人の特徴とトリプトファン・ビタミン B<sub>6</sub>・ニコチンアミド含有サプリメントの食間摂取による抑うつ気分の改善効果)

申請者 辻田 那月

The number of people suffering from depression is increasing, with an estimated 300 million individuals worldwide currently affected. Young adults experience stressful transition from adolescence to adulthood, and the prevalence of depression in young adults is high. Despite these key issues, young adulthood is the least likely age group to have adequate access to mental health services among adult age groups. Therefore, it is important to prevent the appearance of depressive symptoms at an early stage before the onset of clinical depression in young adults.

Previous studies have consistently shown that physical activity (PA) can prevent future depression, and low PA levels are associated with depression onset. Nutritional status, particularly tryptophan (TRP), the only precursor of serotonin, and vitamin B<sub>6</sub>, a coenzyme in the TRP-serotonin metabolic pathway, are also associated with depression. Decreased plasma TRP and vitamin B<sub>6</sub> levels have been reported in depressed patients compared with healthy subjects. The association between depression and cardiovascular disease also suggests involvement of dysfunctional autonomic nervous system (ANS) activity. However, conflicting results have been reported on the precise relationship between depression and ANS activity. This variation may result from ANS activity being influenced by a number of different physiological factors, such as sex, age, medication, PA, and food intake. Differences in research methodology may also influence assessments of ANS activity. Heart rate variability (HRV) is a reliable quantitative marker for the investigation of sympathetic and parasympathetic autonomic activity, as well as sympathovagal balance. Our HRV power spectral analysis is a well-accepted, useful, and noninvasive method for assessing ANS activity.

Although many studies of depressed patients have investigated PA, nutritional status, or ANS activity, because ANS activity is particularly affected by food intake, PA, and medication, these characteristics need to be examined simultaneously for optimal comprehensive studies. Identifying the characteristics of young adults with subclinical depression may facilitate the development of preventive interventions and help to reduce the incidence of depression.

Depressed patients are treated with antidepressants or cognitive behavioral therapy; however, an effective way to alleviate depressive symptoms in subjects with subclinical depression is unknown. TRP is a precursor of serotonin and may have an antidepressant effect. The brain uptake pathway for TRP is shared by other large neutral amino acids (LNAAs), which compete with TRP for transport across the blood-brain barrier (BBB). The normal dietary intake of TRP from protein is lower (<1 g/day) than that of other LNAAs. Thus, protein-rich foods increase LNAAs other than TRP, leading to lowering of the

TRP/LNAA ratio and increasing competition for uptake at the BBB. Therefore, between meals represents the time when the influence of other LNAAs is minimal and TRP is efficiently converted to serotonin. Vitamin B<sub>6</sub> may have a mood-elevating or antidepressant effect and nicotinamide displayed an antidepressant effect in combination with TRP. Therefore, taking TRP between meals with vitamin B<sub>6</sub> and nicotinamide may promote serotonin synthesis and improve mood in young adults with subclinical depression. However, no previous study has specified when TRP should be administered, and its effect remains unclear. Furthermore, it has been reported that TRP causes drowsiness, suggesting that parasympathetic activity is activated, while the influence of TRP on ANS activity is unknown.

Therefore, the aims of this study were: (1) to comprehensively investigate PA, nutritional status, and ANS activity in young adults with subclinical depression, and in sex- and age-matched nondepressed controls, and elucidate any differences between them; and (2) to investigate the beneficial effect of TRP, vitamin B<sub>6</sub>, and nicotinamide-containing supplement loading between meals on mood and ANS activity in young adults with subclinical depression.

### ***First study***

Although many studies of depressed patients have investigated PA, nutritional status, or ANS activity, the literature is currently scarce on available studies examining these characteristics simultaneously in subjects with subclinical depression. The aim of the present study was to comprehensively investigate PA, nutritional status, and ANS activity in young adults with subclinical depression, and in sex- and age-matched nondepressed controls, and elucidate any differences between them.

We recruited 35 young adults with higher levels of depressive symptoms (the DEP group) and 35 sex- and age-matched controls without depressive symptoms (the CON group). The criterion for higher levels of depressive symptoms was the Center for Epidemiologic Studies Depression Scale (CES-D) score of  $\geq 16$ . Study subjects wore activity trackers for 3 days to measure their daily number of steps, and the duration and amount of PA  $\geq 3$  metabolic equivalents (METs). Exercise habits as well as the consumption of TRP and/or vitamin B<sub>6</sub>-rich foods were assessed using an original questionnaire. Plasma levels of total TRP and vitamin B<sub>6</sub> were also determined. ANS activity was assessed using HRV power spectral analysis. Nutritional status was assessed using a Food Frequency Questionnaire based on food groups.

The DEP group had fewer daily steps as well as duration and amount of PA  $\geq 3$  METs than the CON group, while there was no difference in exercise habits. The estimated energy intake in the DEP and CON groups was nearly identical. Contrary to expectations, the intake frequency of TRP and/or vitamin B<sub>6</sub>-rich foods of the DEP group was higher than that in the control group, and plasma vitamin B<sub>6</sub> levels in the DEP group were significantly higher than those in the CON group, while plasma TRP levels were comparable between the two groups. No significant between-group differences were observed with respect to any of the HRV indices. The CES-D scores displayed a significant negative correlation with steps, duration, and the amount of PA  $\geq 3$  METs. On the other hand, a positive correlation was found between the CES-D scores and plasma vitamin B<sub>6</sub> levels.

Our findings suggest that a decline in overall PA, including daily steps and the duration and amount of moderate-to-vigorous PA, could be associated with subclinical depression in young adults. Their dietary intake of TRP and/or vitamin B<sub>6</sub>-rich foods was adequate, and they displayed no ANS activity dysfunction.

### ***Second study***

TRP, a precursor of serotonin, is believed to have an antidepressant effect. The brain uptake pathway for TRP is shared by other LNAAs, which compete with TRP for transport across the BBB. Therefore, between meals represents the time when the influence of other LNAAs is minimal and TRP is efficiently converted to serotonin, but no previous study has specified when TRP should be administered, and its effect remains unclear. Furthermore, the influence of TRP on ANS activity is unknown. Vitamin B<sub>6</sub> and nicotinamide are known to enhance the effects of TRP. This study investigated the beneficial effect of TRP, vitamin B<sub>6</sub>, and nicotinamide-containing supplement loading between meals on mood and ANS activity in young adults with subclinical depression.

Thirty young adults with subclinical depression were randomly allocated to receive 100 mg of TRP, 4 mg of vitamin B<sub>6</sub>, and 4 mg of nicotinamide-containing supplement or a placebo supplement twice daily between meals (i.e., between breakfast and lunch and between lunch and supper) for 7 consecutive days. Depressive symptoms were defined as being present when subjects had a CES-D score of  $\geq 16$ . Depressive symptoms and mood were measured using the CES-D and the Profile of Mood States (POMS), respectively, before and after the intervention. ANS activity was analyzed by HRV power spectral analysis. Blood samples were assayed for plasma total TRP levels. For analysis, TRP and placebo groups were further classified into two subgroups according to CES-D score (mild to moderate vs. severe depressive symptoms).

The CES-D score significantly improved following both treatments in the severe depression subgroups, while the POMS depression score was significantly improved only in the TRP severe depression subgroup. For the other POMS subscales, no differences were found between supplements. There was also no significant change in ANS activity or plasma total TRP levels in any group.

Thus, TRP, vitamin B<sub>6</sub>, and nicotinamide-containing supplement loading between meals can quickly improve depressive mood in quite low doses in young adults with severe subclinical depression.

In summary, through these two studies, we investigated the characteristics of young adults with subclinical depression and the beneficial effect of TRP, vitamin B<sub>6</sub>, and nicotinamide-containing supplement loading between meals on their mood and ANS activity. In the ***first study***, we found that young adults with subclinical depression had only a decline in overall PA. Their dietary intake of TRP and/or vitamin B<sub>6</sub>-rich foods was adequate, and there was no ANS activity dysfunction. In the ***second study***, we found that TRP, vitamin B<sub>6</sub>, and nicotinamide-containing supplement loading between meals can quickly improve depressive mood in quite low doses in young adults with severe subclinical depression. These results clearly indicate that (1) young adults with subclinical depression are characterized by decreased PA, and (2) the depressive mood can be ameliorated in a short period of time by TRP, vitamin B<sub>6</sub>, and nicotinamide-containing supplement loading between meals.