

# Levodopa on decrease of plasma taurine level in parkinson's



**Title:**

Levodopa aggravates the decrease of plasma taurine level in Parkinson Disease

**Key words:**

Parkinson's disease (PD); Oxidative stress; Levodopa; Toxicity; Taurine;

**Highlights:**

- This is the first study to explore chronic use of levodopa on the change of plasma taurine level.
- Plasma taurine levels were significantly lower in both treated and untreated PD than in healthy controls.
- Much lower plasma taurine level was found in treated PD than the untreated.
- Plasma taurine level was negatively associated with cumulative dosage of levodopa in PD.

**Abbreviations:**

PD, Parkinson's disease; MMSE, mini-mental state examination; DA, dopamine; ROS, reactive oxygen species; MAO, monoamine oxidase; CNS, central nervous system; H<sub>2</sub>O<sub>2</sub>, peroxide; SOD, superoxide dismutase; CSF, cerebrospinal fluid;

**Abstract**

In recent years, it has gained more and more focus that oxidative stress is implicated in the pathophysiology of Parkinson's disease(PD) as well as the <https://assignbuster.com/levodopa-on-decrease-of-plasma-taurine-level-in-parkinsons/>

potential toxicity of levodopa to nigral cells. Also, an increasing body of evidence suggests that taurine plays an important role in anti-oxidant function. This study aimed to investigate the relationship between plasma taurine level and clinical variables and the cumulative dosage of levodopa in PD patients. 44 treated patients with PD (all receive levodopa), 68 untreated patients with PD and 96 age-and sex-matched healthy controls were recruited. Clinical data such as age, gender, duration, Hoehn and Yahr stage and medication history were collected. Approximate cumulative dosage of levodopa was calculated to indicate the toxicity of chronic intake of levodopa. Plasma levels of taurine were measured by HPLC-RF. Plasma taurine levels were significantly lower in both treated and untreated PD than healthy controls. Much lower plasma taurine level was found in treated PD than the untreated. Furthermore, plasma taurine level was negatively associated with cumulative levodopa dosage in PD. Our preliminary study indicates that taurine may play an important role in pathophysiology of PD and toxicity of chronic levodopa treatment.

## Introduction

PD is the second most common neurodegenerative disorder characterized by selectively loss of dopamine (DA)-containing neurons in the substantia nigra and a concomitant reduction of DA in the striatum. Levodopa, a natural precursor of DA, has been the 'gold standard' therapy for PD patients for decades [1]. However, the pathophysiology of PD is up to now still poorly understood.

More and more focus comes to that oxidative stress is implicated in the pathophysiology of PD, manifested as protein oxidation, lipid peroxidation, DNA oxidation and so on [2]. Moreover, there has been an increasing concern that levodopa may be toxic to dopaminergic neurons [3-5], mainly because of its potential to autoxidize from a catechol to a quinone and to generate other forms of reactive oxygen species (ROS) [6].

Taurine, an endogenous amino acid (2-aminoethanesulfonic acid), is abundant in excitable tissues such as brain, retina, cardiac muscle and skeletal muscle [7]. Both in vitro and in vivo studies together demonstrate that the anti-oxidative activity of taurine is a vital avenue of cytoprotection [8-12]. Additionally, our previous study has reported that plasma taurine level was decreased in patients with PD [13]. Also, there are lines of evidence that taurine may exhibit cytoprotective effect by acting as a scavenger for harmful free radicals produced by DA or levodopa [14, 15].

However, the precise anti-oxidative mechanism of taurine involved in both PD pathophysiology and putative toxicity of levodopa still remains uncertain. Furthermore, few studies have been done to address the relationship between plasma taurine level and clinical variables as well as the toxic effects of chronic levodopa administration. Hence, in our study, we specifically explored the underlying impact on plasma taurine level because of long-term levodopa intake in PD patients.

## 2. Patients and methods

### 2.1 patients

Patients with PD, diagnosed based on UK Parkinson's disease Brain Bank criteria by two movement disorders specialists (Kezhong Zhang and Lian Zhang), were included in this study [16]. Clinical data were collected by the same medical worker and the Hoehn and Yahr stage was used to evaluate the severity of disease [17]. Since the anti-parkinsonian drugs may affect plasma taurine level, thorough medication histories were completely obtained through family and patient recall, personal medical chart, as well as computerized patient information system in our hospital. Exclusion criteria were atypical or secondary Parkinsonism, impaired cognitive status (assessed by the mini-mental state examination (MMSE) [18]), previous neurosurgical treatment for PD, significant laboratory, medical, or psychiatric abnormalities, or any condition that might affect plasma taurine level. Age- and gender-matched controls were also recruited, devoid of neurological disease, poor nutritional status, dementia or a family history of PD. The research project was approved by the ethics committee of the first affiliated hospital of Nanjing medical university and all the participants were given a full explanation and consented to the study in writing.

## 2. 2 Calculation of the cumulative levodopa amount

In order to assess the underlying toxicity of levodopa, an approximation of the cumulative levodopa amount was calculated based on the following equation (modified according to that of Nagatsu et al. [19]): cumulative levodopa amount [g] = daily amount of levodopa [mg] \* duration of levodopa intake [month] \* 30 [d/month] \* 0.001 [g/mg].

## 2. 3 Measurement of taurine levels from plasma

<https://assignbuster.com/levodopa-on-decrease-of-plasma-taurine-level-in-parkinsons/>

Plasma taurine levels were measured as previously described [13].

## 2. 4 Statistical analysis

All statistical analyses were performed in SPSSV. 20. 0 (SPSS, Chicago, IL, USA). The normality of the distribution of all continuous variables was examined by Shapiro–Wilk statistic. Homogeneity of variance was assessed by Levene’s test. Group comparisons were made using chi-square test for categorical variables, and one-way ANOVA as well as the Kruskal-Wallis test which was followed by the Mann-Whitney U test with Bonferroni correction for multiple comparisons (controls vs untreated patients, controls vs treated patients, untreated patients vs treated patients), as appropriate, for continuous variables. The correlation significance was evaluated by Spearman rank correlation coefficient. The statistical significance was set at  $P < 0. 05$ .

## 3. Results

### 3. 1. Demographic data, clinical variables and treatment status of PD Patients and Controls

The demographic and clinical data of all subjects are summarized in Table 1. Gender and age did not differ among three groups, while the duration was longer ( $2. 90 \pm 1. 50$  vs.  $1. 45 \pm 1. 14$  y,  $p < 0. 001$ ) and the Hoehn and Yahr stage was higher ( $1. 97 \pm 0. 71$  vs.  $1. 67 \pm 0. 72$ ,  $p < 0. 05$ ) in treated PD than untreated PD. Within treated PD, all the patients received levodopa drugs. In addition to levodopa therapy, treated patients also received DA agonists,

monoamine oxidase (MAO) inhibitors, or adamantanamine (fordetailed information on the treatment status see Table 2).

### 3. 2. Plasma taurine level in PD patients and controls

Notably, bothtreated PD ( $41.16 \pm 22.72 \mu\text{mol/L}$ ) and untreated PD ( $57.38 \pm 31.05 \mu\text{mol/L}$ ) were found to have significantly decreased plasma taurine levels compared to healthy controls ( $133.83 \pm 45.91 \mu\text{mol/L}$ , P for both comparisons  $<0.001$ ). Moreover, plasma taurine level was even lower in treated PD than untreated PD (shown in Fig. 1, P  $<0.001$ ). When datafor the two PD groups were considered as a whole, the mean taurine level was also significantly lower than that in the control group (P  $<0.001$ ). No significant differences between genders for taurine levels were found in treated PD, untreated PD, all PD, or healthy controls (data not shown).

### 3. 3. Association between plasma taurine level and clinical variables and treatment status.

Plasma taurine levels showed, however, no statistically significant association with age, duration, as well asHoehn and Yahr stage in treated PD, untreated PD or all patients (Data not show). Interestingly, significant correlation was found between taurine level and cumulative levodopa dosage (shown in Fig. 2,  $r_s = -0.351$ , P  $<0.05$ ).

## Discussion

According to our knowledge, this is the first study to explore chronic use of levodopa on the change of plasma taurine level. The major results of this

study are summarized as follows: 1) Treated and untreated PD were found to have significantly decreased plasma taurine levels compared to healthy controls. 2) Plasma taurine level was lower in treated PD than the untreated, and inversely correlated with cumulative dosage of levodopa.

Taurine, the most abundant amino acid in mammals, is widely distributed in central nervous system (CNS) [20] and its biosynthesis mainly takes place in the liver [21]. In the CNS, the concentration of taurine is dependent on food and a complex transport system at the blood brain barrier [20]. Hence, plasma taurine may partially reflect the pathological change in CNS of PD patients.

Firstly, decreased plasma taurine level of patients with PD observed in this study is in line with our previous work [13]. Similarly, there have been some studies reporting CSF (cerebrospinal fluid) taurine level was significantly decreased in PD when compared to healthy controls [19, 22]. Previous studies provide evidence that taurine has a remarkable anti-oxidative function. Furthermore, in a study of PC12 cells, taurine exhibited a protective role against oxidative stress induced by peroxide ( $H_2O_2$ ) through the alleviation of endoplasmic reticulum stress [12]. Also, Castro-Caldas et al. [10] reported that pretreatment of TUDCA (an analogue of taurine) abrogated the level of ROS in MPTP-mice, thus further highlighting the anti-oxidative role in vivo and suggesting that TUDCA may modulate the intracellular oxidative environment via interfering with the cellular redox threshold. Moreover, it has been observed that significant increases in glutathione content and superoxide dismutase (SOD) activity were founded in the livers of the taurine-supplemented 6-OHDA-induced PD rats, which <https://assignbuster.com/levodopa-on-decrease-of-plasma-taurine-level-in-parkinsons/>



indicated that taurine may increase the defenses against oxidative insult [11]. Collectively, we assume that the decrease of plasma taurine level may result from chronic assumption of oxidants. Therefore, taurine may play an important neuroprotective role in the pathophysiology of PD via its potent anti-oxidative activity.

By contrast, both normal [23] and increased [24-26] CSF taurine levels were found in several previous studies. Moreover, no significant decreased plasma taurine was observed in Molina et al.'s study [22]. However, studies conducted by Lakke et al. [25, 26], Tohgi et al. [23] and Araki et al. [24] all had some limitations. For example, the controls were not well matched regarding gender and age. Additionally, different sample sizes and measurements may also partially explain the discrepancy of the results. Compared with those previous studies, we recruited relatively more patients in this study. Also, statistical analysis was well performed and measurement used in our study is more stable and sensitive.

Nevertheless, we fail to observe correlation between plasma taurine level and age, duration and Hoehn and Yahr in treated PD, untreated PD or all PD. This may result from that only patients with relatively short duration (within 5 years) and low Hoehn and Yahr (within stage 3) were enrolled in our study, and the plasma taurine was probably not sensitive enough to examine the underlying correlation in early to medium stage PD patients. Therefore, further research including more stages of patients would bring more invaluable information on this point.

Secondly, treated PD patients exhibited lower plasma taurine level than the untreated. Although the duration was longer and the Hoehn and Yahr stage was higher in treated PD than untreated PD, neither of the two clinical variables was correlated with plasma taurine level in each group. More importantly, plasma taurine level significantly negatively correlated with cumulative dosage of levodopa. These data suggest that chronic treatment of levodopa may affect plasma taurine concentration.

Previous studies have shown that levodopa has the capacity to form ROS by autoxidation from catechols to quinines [4]. Interestingly, Biasseti et al. [27] found that taurine attenuated iron-catalyzed quinone formation from levodopa. Also, some studies suggest that taurine may bind these toxic quinones [27, 28]. Furthermore, there have been studies [29] showing that chronic systemic administration of levodopa to rodents depleted taurine pools, suggesting that taurine might play an important role in scavenging oxidants derived from levodopa metabolism in vivo. Therefore, we suppose that chronic consumption of taurine due to oxidants induced by levodopa may partially explain lower plasma taurine level in levodopa-treated PD than the untreated.

However, there were different results observed in some other studies. Molina et al. [22] reported that no significant difference of CSF taurine level was found between levodopa-treated PD (n= 21) and non-levodopa-treated PD (including untreated PD, n= 8). The relatively small sample size may limit its interpretation. Moreover, Diederich et al. [30] found no significant decrease of plasma taurine after acute administration of levodopa. However, the acute

levodopa administration may not fully reflect the toxicity of cumulative levodopa intake.

Nevertheless, our study has some limitations. Firstly, the population in this study is relatively small and the results must be interpreted cautiously. Secondly, as this is only a retrospective study, future longitudinal study combining with biomarkers of oxidative stress will provide more important information on the role of levodopa in affecting the plasma taurine level as a neurotoxic agent and of taurine as an anti-oxidative agent.

In conclusion, our results showed that decreased plasma taurine level was found in patients with PD in comparison to healthy controls. Moreover, plasma taurine level was found lower in treated PD than the untreated, and inversely correlated with cumulative levodopa dosage. Combining with previous studies, these data suggest taurine may play an important protective role in pathophysiology of PD and chronic administration of levodopa may have potential neurotoxicity by depleting taurine. Also, our pilot study could, at least, provide new insights into therapeutic strategies.