

## Effects of concurrent training and CoQ10 on neurotrophic factors and physical function in people with Multiple Sclerosis: a pilot study

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### Abstract

The present study aimed to investigate the effects of 8-week of coenzyme Q10 (CoQ10) supplementation alone or combined with concurrent training (CT) on functional capacity, serum brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in multiple sclerosis (MS) patients. Our hypothesis is that CT promotes improvements in the studied outcomes with higher results for the combination of CT and CoQ10. Randomized placebo-controlled trial. Twenty-eight patients with MS were randomly divided into 4 groups: CT+placebo, CT+CoQ10, CoQ10 and placebo. CT involved two resistance training sessions and one aerobic training session per week. CoQ10 was supplemented with 200 mg daily. Serum levels of BDNF, NGF and functional tests [timed up and go (TUG), 6-min walk (6MW), chest press, lateral pull down, leg extension, and lying leg curls one repetition maximum] were measured before and after the intervention period. CT+placebo and CT+CoQ10 significantly improved performance in TUG, 6MW, chest press, lateral pull down, leg extension, and lying leg curls, with superior results to both CoQ10 and placebo groups. Changes in TUG for CT+placebo were significantly higher than CT+CoQ10 ( $p < 0.05$ ). There were no significant differences in NGF and BDNF among the four groups ( $p > 0.05$ ). CT improves physical abilities in patient with MS, regardless CoQ10 supplementation. CT should be recommended for MS patients to increase functional capacity, but there seems to be no benefit in supplementing CoQ10.

**Key Words:** Multiple sclerosis; neurodegenerative disease; exercise therapy; NGF; BDNF; resistance training; interval training; ubiquinone.

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Multiple sclerosis (MS) is the most common debilitating neurological disease among adults.<sup>1</sup> MS is an autoimmune central nervous system disorder characterised by demyelination and neurodegeneration that leads to physical disability.<sup>2</sup> Previous researches examined nutritional strategies that are potentially effective for MS management.<sup>3,4</sup> Given the important role of inflammation, oxidative stress and mitochondrial dysfunction in MS development, treatments with anti-inflammatory and antioxidant supplements have received growing attention.<sup>5,6</sup> Among them, coenzyme Q10 (CoQ10) is considered a promising therapeutic agent in neurodegenerative diseases. The administration of

CoQ10 alone or in combination with other substances in mice with induced-neurodegenerative disease provided neuroprotective effects such as decreased brain oxidative stress and damage, as well as increased neurotrophic factors (e.g., BDNF).<sup>7,8</sup> CoQ10 supplementation might be of potential interest due to its anti-inflammatory and antioxidant effects in MS patients,<sup>9</sup> as well as its positive effects on fatigue and depressive symptoms.<sup>10</sup> Physical exercise is also a potential therapeutic strategy for managing MS, and is considered safe and effective, with positive effects in fitness, functional capacity and quality of life.<sup>11</sup> Exercise exerts its positive therapeutic effects through different pathways. It increases regeneration of sensory neurons after axonal injury, stimulates the

expression of genes associated with axon growth and regeneration, and improves nerve function.<sup>12,13</sup> Physical exercise can also reduce MS symptoms by improving motor coordination, aerobic capacity and muscle strength.<sup>14</sup> Moreover, physical exercise has been shown to increase the expression of neurotrophic factors such as brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF).<sup>15,16</sup> Although many different strategies have been used, the combination of resistance and aerobic training, known as concurrent training (CT), has been shown to be particularly beneficial for people with MS.<sup>17,18</sup> Considering the potential benefits of CoQ10 supplementation in MS, it is plausible to suggest that it might exert additional effects when combined with CT. Therefore, the aim of the present study was to investigate the effects of eight weeks of a CT and CoQ10 supplementation on physical function, serum BDNF and NGF levels in people with MS. Our hypothesis is that CT would promote improvements in the studied outcomes with higher results for the combination of CT and CoQ10.

**Materials and Methods**

**Participants**

The study involved 28 MS patients, among 3243 members of the Multiple Sclerosis Association of Mashhad (Iran).

Inclusion criteria were: 1) MS diagnosis according to 2017 McDonald criteria;<sup>19</sup> 2) Expanded Disability Status Scale (EDSS) between 2 and 5; 3) No smoking history; 4) No history of regular exercise; 5) At least 2 years of stable disease modifying treatment; 6) Aged higher than 18 and lower or equal 4. We opted to select younger participants to avoid the confounding effects of age in the studied outcomes.

Exclusion criteria: 1) MS relapse within 30 days from patient enrolment; 2) Moderate to severe cardiovascular disease (Stage III or IV, according to the New York Heart Association); 3) Any other condition that could be aggravated by the study protocol.

This study was approved by relevant Ethics Committee and registered at Clinical Trials records (2019-08-11, 1398/05/20). All subjects or their parents provided a written informed consent prior to study participation. The study was performed in accordance with good clinical practices and Declarations of Helsinki.

**Study procedures**

Participants were divided into four groups: CT+placebo, CT+CoQ10, CoQ10, and placebo using a simple random method (lottery). Participants in the CoQ10 and placebo groups did not engage in any form of physical exercise during the study. CoQ10 was manufactured by Nutri Century (Canada) and ingested as one 200 mg capsule daily. Starch powder was used as placebo and its

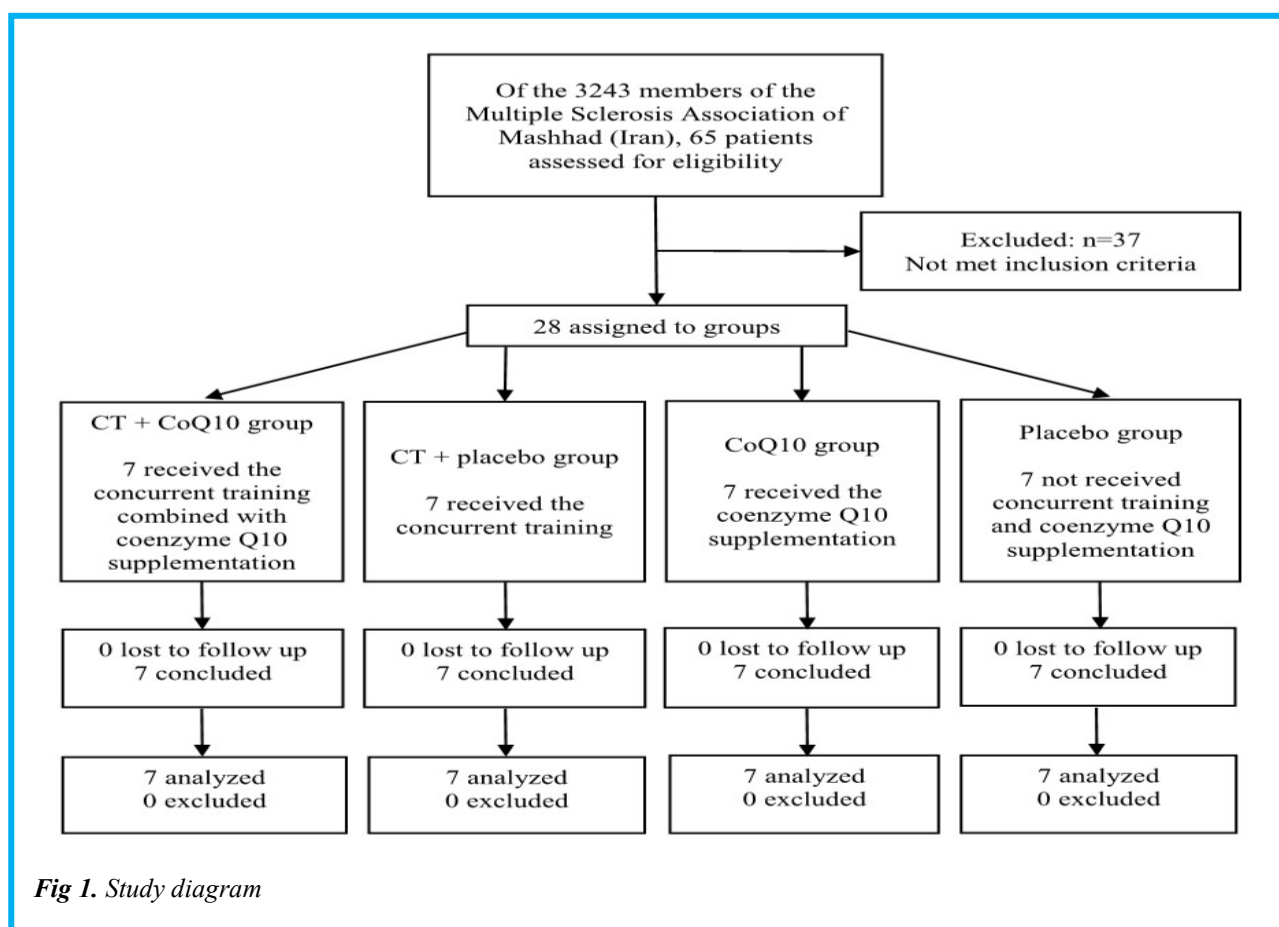


Fig 1. Study diagram

**Table 1.** Demographic and clinical features for enrolled subjects according to treatment group.

	CT + CoQ10 (n=7)	CT + placebo (n=7)	CoQ10 (n=7)	Placebo (n=7)	p-value
Gender					
Men (%)	4 (57.14)	4 (57.14)	4 (57.14)	4 (57.14)	1.000
Women (%)	3 (42.86)	3 (42.86)	3 (42.86)	3 (42.86)	
Age, years					
median (Q1-Q3)	41.00 (40.00-45.00)	32.00 (28.00-45.00)	35.00 (32.00-44.00)	36.00 (31.00-44.00)	0.448
Weight, kg					
mean ± standard deviation	68.64 ± 3.70	66.50 ± 3.01	67.94 ± 2.21	68.50 ± 1.21	0.445
Height, cm					
mean ± standard deviation	167.00 ± 3.83	162.14 ± 4.63	163.71 ± 5.68	165.43 ± 4.54	0.270
History of MS, years					
mean ± standard deviation	5.86 ± 1.35	4.86 ± 1.07	4.86 ± 2.03	4.86 ± 1.57	0.543
EDSS, score					
mean ± standard deviation	3.69 ± .052	3.79 ± 0.39	3.64 ± 0.75	3.64 ± 0.69	0.967
VO <sub>2Peak</sub> (ml/kg/min)					
mean ± standard deviation	25.27±1.00	24.93±0.89	24.29±1.74	24.26±0.50	0.278

MS = Multiple sclerosis; EDSS = Expanded disability status scale

consumption was similar to the consumption of CoQ10 supplements. The study diagram is presented in Figure 1.

### Exercise protocol

CT was performed three sessions per week (two resistance training sessions and one aerobic training session) for eight weeks. Every session started with a 5-10 minutes warm-up and ended with 5-10 minutes cool down. Resistance training involved chest press, lateral pull down, leg extensions, and lying leg curls using a minimal dose approach. Exercises were performed in three sets of eight to 10 repetitions at 50-60% of one repetition maximum (1RM), 2-3 minutes rest between sets and 3-4 minutes between exercises.

Aerobic exercises included moderate intensity interval training on a cycle ergometer. Training involved 5 to 12 bouts of 3 minutes interspersed by 1 minute of passive recovery. For exercise prescription, VO<sub>2peak</sub> was estimated through the Astrand bicycle aerobic test.<sup>20</sup> Aerobic training started with 5 bouts at 50% of the peak oxygen consumption (VO<sub>2peak</sub>) in the first week and ended with 12 bouts at 60% VO<sub>2peak</sub>.

### Blood analysis

Blood samples (5 cc) were collected 24 hours before the beginning of the study and 24 hours after the last training session, after 10 hours overnight fasting. Women were evaluated in the follicular stage (first 3 to 5 days of the cycle). BDNF (Human BDNF Elisa kit, Boster Biological Technology Co) and NGF concentration (Human NGF Elisa kit, Boster Biological Technology Co) were measured with ELISA method using specific kits.

### Functional tests

Timed up and go (TUG) and 6-min walk (6MW) tests were used to evaluate physical functioning. Muscle strength was evaluated by estimated 1RM on chest press, lateral pull down, leg extension, and lying leg curls. Tests were performed in the beginning (24 hours before the first training session) and in the end of study period (48 hours after the last training session). All tests were performed using the same procedures and supervised by the same investigator, that was blind to group allocation. For TUG, participants stand up from a standard armchair,

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**Table 2.** Outcome measures pre- and post- treatment.

	Groups	Baseline	Follow-up	F	p-value	ES
Daily calorie intake (kcal) mean± standard deviation	CT + CoQ10	1977.90±181.97	2068.30±146.99	0.175	0.912	0.022
	CT + placebo	2029.30±217.56	2009.00±242.11			
	CoQ10	2063.40±119.47	2056.90±189.65			
	Placebo	2080.30±151.63	1996.40±168.59			
BDNF (ng/ml) mean± standard deviation	CT + CoQ10	2.94±0.27	2.92±0.15	0.345	0.793	0.041
	CT + placebo	2.81±0.42	2.81±0.47			
	CoQ10	2.89±0.13	3.04±0.16			
	Placebo	2.98±0.10	2.98±0.25			
NGF (pg/ml) mean± standard deviation	CT + CoQ10	376.14±41.38	399.00±54.02	0.267	0.849	0.034
	CT + placebo	394.80±38.55	385.17±76.82			
	CoQ10	399.23±22.38	413.17±61.81			
	Placebo	428.23±105.56	407.46±34.79			
Time up and go (s) mean±standard deviation	CT + CoQ10	7.70±0.71	**6.79±0.51	23.262	‡<0.001	0.752
	CT + placebo	8.15±0.74	***6.55±0.47			
	CoQ10	7.70±0.52	7.66±0.61			
	Placebo	7.61±0.71	7.72±0.92			
6-min walk (m) mean±standard deviation	CT + CoQ10	272.14±6.26	***303.29±11.34	19.110	‡<0.001	0.714
	CT + placebo	269.57±18.68	**294.71±27.18			
	CoQ10	271.00±16.71	270.14±16.49			
	Placebo	266.14±13.26	267.76±10.17			
Chest press (kg) mean±standard deviation	CT + CoQ10	23.78±1.70	**31.38±2.98	26.933	‡<0.001	0.788
	CT + placebo	23.51±3.43	***31.73±3.05			
	CoQ10	24.65±2.05	24.87±2.01			
	Placebo	24.52±2.17	24.66±2.79			
Lateral pull down (kg) mean±standard deviation	CT + CoQ10	22.70±1.78	***26.01±1.43	17.111	‡<0.001	0.691
	CT + placebo	22.27±2.55	***25.92±1.76			
	CoQ10	21.76±2.31	22.29±2.97			
	Placebo	20.91±2.40	21.47±2.19			
Leg extension (kg) median (Q1-Q3)	CT + CoQ10	12.00(11.61-13.36)	*16.87(15.88-17.42)	16.869	†0.001	0.578
	CT + placebo	12.41(10.90-13.33)	*16.87(15.88-18.62)			
	CoQ10	12.86(12.41-13.33)	*12.86(12.86-16.87)			
	Placebo	12.41(11.61-13.33)	12.00(12.00-13.33)			
Lying leg curls (kg) median (Q1-Q3)	CT + CoQ10	12.00(11.61-12.86)	*16.36(16.36-17.42)	21.395	‡<0.001	0.766
	CT + placebo	12.41(10.90-13.33)	*17.42(16.87-18.62)			
	CoQ10	12.00(11.61-13.33)	12.00(12.00-13.33)			
	Placebo	12.00(11.25-13.33)	12.00(11.61-12.86)			

\*  $p$ -value<0.05, \*\*  $p$ -value < 0.01, \*\*\*  $p$ -value<0.001, by paired-samples  $t$  test and Wilcoxon; †  $p$ -value < 0.01, ‡  $p$ -value<0.001, by analysis of variance, Kruskal-Wallis, analysis of covariance tests

walked three meters as fast as possible, turned back, walked back to the chair, and sited down again. The test was performed twice, and the best result was used in the analysis. The 6MW test consisted in walking

continuously as fast as possible around a 30 meters track for six minutes and the final distance achieved was recorded in meters. To calculate IRM, participants performed each exercise to momentary muscle failure,

then 1RM was estimated using the Brzycki formula (21). During all tests participants were verbally encouraged to give their maximum effort.

**Dietary analysis**

Dietary information was collected during the first and last study week using a 24-hour food recall questionnaire for three days. Data was analysed using Nutrition 4 software (First Databank, San Bruno, CA, USA).

**Statistical analysis**

Sample size (n=28) was estimated using G\*Power software v3.1.9.4, with alpha coefficient of 0.05, statistical power of 0.80, and effect size of 0.5, based on previous research. All analyses were conducted using SPSS software (Statistical Package for Social Sciences Chicago, IL, USA) version 20.0. Normal distribution for continuous variables was explored through Shapiro-Wilk test. Changes for BDNF, NGF, timed up and go, 6-min walk, chest press, lateral pull down, leg extension, and lying leg curls between baseline and follow-up were analysed through paired-samples t test and Wilcoxon. The analysis of variance (ANOVA), Kruskal-Wallis, analysis of covariance (ANCOVA) tests were used to compare groups. The LSD and Gamese-Howell tests were used for post hoc comparisons were necessary. Results were considered statistically significant when p <0.05.

**Results**

Participants’ demographic and clinical characteristics are shown in Table 1. There was no significant difference within or between groups for daily calorie intake (Table 2). CT+CoQ10 and CT+placebo groups showed significant improvements in TUG (p<0.01), 6MW (p<0.01) and on 1RM loads for chest press (p<0.01), lateral pull down (p<0.01), leg extension (p<0.01), and lying leg curls (p<0.01). CoQ10 group showed a significant improvement only in 1RM leg extension (p<0.05). NGF and BDNF levels did not change for any

group (Table 2). All indicators of functional capacities improved at post intervention for CT+CoQ10 and CT+placebo groups compared to CoQ10 and placebo groups. There was a significant difference (p=0.011) in TUG between CT+CoQ10 and CT+placebo, with greater changes for CT+placebo than CT+CoQ10 (Figure 2).

**Discussion**

The present study aimed to investigate the effects of eight weeks of CT and CoQ10 supplementation, alone or combined, on physical function, serum BDNF and NGF levels in people with MS. As our main result, CT with or without CoQ10 supplementation, significantly improved physical capacity in MS patients, without changes in NGF and BDNF. Our results are in agreement with previous studies showing that CT improves physical function in patients with MS and might help to manage the negative effects of MS on physical disability and quality of life.<sup>22,23</sup> Similarly to our study, Grazioli et al.<sup>17</sup> reported that 12 weeks of CT significantly improved TUG and 6MW test in patients with MS. Moreover, Bahari et al.<sup>24</sup> reported that eight weeks of CT increased strength and balance in patients with MS. Resistance training has been introduced to improve muscle function, specially for its effects on neural adaptations.<sup>25</sup> Increasing lower limbs strength might help to counteract motor fatigue and affects sensory and peripheral nerve pathways or both, leading to improvements in walking speed, endurance and economy.<sup>26</sup> Another important effect of resistance training in MS is the increase in maximal neural drive and neural plasticity.<sup>27</sup> The combination of increased motor units recruitment, movement economy, reductions on inhibitory inputs from alpha motor neurons can be among the factors responsible for increasing muscle adaptations observed in the present study.<sup>25</sup> One factor that might have mediated functional improvements was balance. There is a direct and significant relationship between lower body muscle strength and balance, such that muscle weakness leads to reduced balance and increased risk of falling.<sup>28</sup>

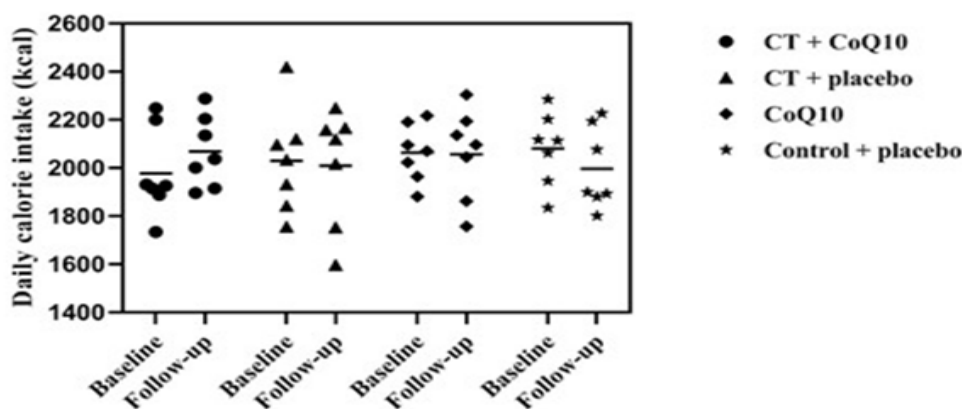


Fig 2. Indicators of functional capacities

In the present study muscles strengthening due to both resistance training and cycling,<sup>29</sup> might have impact balance in these patients. Specifically, resistance exercises might improve balance in MS patients by reducing muscle spasms and sensory disturbances.<sup>30</sup> While previous authors found positive effects of cycling in MS,<sup>31-34</sup> the mechanism are not fully understood, but might be associated with general improvements in muscle function and physical fitness.<sup>32-34</sup> Lower limb muscle strength is related to walking speed and is an important predictor of motor performance in MS patients.<sup>35</sup> Resistance exercises has been shown to improve walking kinematics in persons with MS,<sup>36</sup> leading to improvement in the performance of 6-min walk test. Moreover, exercise has been shown to increase endorphin levels and improvement psychological factors, which could influence fatigue and improve motor performance.<sup>37</sup> Regarding neurotrophic factors, Abbaspoor et al.<sup>38</sup> showed that BDNF levels did not change after eight weeks of exercise training. Similarly, Khademosharie et al.<sup>39</sup> showed that CT did not cause significant differences in NGF and BDNF levels of patient with MS. However, different from the present findings, previous studies demonstrated that CT increased BDNF levels in patient with MS.<sup>40,41</sup> It is difficult to explain this divergence, since the mechanism involved in exercise-induced BDNF concentration is not well known. These differences and inconsistencies might be due to the type and intensity of exercise, the length of the training period, differences in research samples, supplementation dose and duration. Although the benefits of CT are of clinical importance and reinforce previous findings, a major novelty of the present study is the combined supplementation of CoQ10, which has been hypothesized to reduce inflammation and oxidative stress in MS patients.<sup>42</sup> Contrary to our hypothesis, there was no benefit in supplementing CoQ10 in the present study, alone or combined with CT, in physical function and NGF and BDNF levels. Based on these findings, CT should be recommended to help in MS management specially for its potential benefits for improving physical function, but this was not the case for CoQ10 supplementation. Low dose CoQ10 supplementation (200 mg daily) or short duration of CoQ10 supplementation period (eight weeks) may have limited the possibility of observing CoQ10 effects on motor abilities and neurotrophic factors. Therefore, longer intervention periods and higher CoQ10 doses should be further investigated in future research. The absence of changes in NGF and BDNF levels may be due to the small sample size. Although we conducted an a priori analysis for samples size, we could not exclude the possibility of type II error in the present study. Consequently, studies with larger samples might be needed to corroborate our findings. Other limitations that can be mentioned in this research are: the lack of precise control of activities outside the training protocol and drugs used by these patients.

### List of acronyms

1RM – one repetition maximum  
6MW - 6-min walk  
ANCOVA – analysis of covariance  
BDNF – brain derived neurotrophic factor  
CoQ10 – Coenzyme Q19  
CT - concurrent training  
MS – multiple sclerosis  
NGF – nerve growth factor  
TUG - timed up and go

### Contributions of Authors

Conceptualization, AHH and AA; methodology, AHH, AA, RA, KN, BBR, HS; formal analysis, AHH, AA, RA, KN, BBR, HS; writing—original draft preparation, AHH, AA, AC, RA, KN, BBR, HS, DS and PG—review and editing, AHH, AA, AC, RA, KN, BBR, HS, DS and PG; visualization, AHH, AA, AC, RA, KN, BBR, HS, DS and PG. Authors approved the final typescript.

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### Conflict of Interest

The authors declare no financial, personal, or other conflicts of interest.

### Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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