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Original Article

The effects of resistance exercise and leucine-enriched essential amino acid supplementation on muscle mass and physical function in post-gastrectomy patients: a pilot randomized controlled trial

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Abstract. [Purpose] In gastric cancer patients, low muscle mass decreases overall survival and quality of life (QOL). Resistance exercise with leucine-enriched essential amino acid (LEAA) supplementation may prevent muscle mass loss. This study was aimed at determining whether resistance exercise with LEAA supplementation prevents muscle mass loss in post-gastrectomy patients. [Participant and Methods] We conducted a single-center, open-label, randomized controlled pilot trial. Ten participants who underwent gastrectomy were divided into two groups. The intervention group underwent resistance exercise at 70% of one repetition maximum and received a supplement of 3 g of LEAA twice daily for 15 days, while the control group received standard care. We compared changes in muscle mass, physical function (muscle strength and continuous walking distance), and QOL between the groups. [Results] We found good adherence and participation rates in both groups. We failed to detect a significant difference in muscle mass between the groups. The intervention group showed significant improvements in muscle strength and QOL, while the control group showed no significant changes. [Conclusion] We failed to detect a significant difference in muscle mass due to resistance exercise with LEAA supplementation in post-gastrectomy patients. However, resistance exercise with LEAA supplementation might be beneficial for muscle strength recovery and QOL improvements.

Key words: Resistance exercise, Leucine-enriched essential amino acids (LEAAs), Gastrectomy

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INTRODUCTION

In recent years, cancer patients' quality of life (QOL) has become an important issue because of increased survival rates. Reducing weight and muscle mass strongly influences the QOL in cancer patients[1]; therefore, preventing weight and muscle mass loss has become essential.

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Stomach cancer is prevalent, with more than one million new cases annually2). Patients who undergo total gastrectomy for stomach cancer experience a significant decrease in weight and muscle mass during the first month after surgery3). In post-gastrectomy patients, low muscle mass is a critical factor for overall survival4), severe postoperative complications5), and QOL6). For these reasons, preventing muscle mass loss is critical for post-gastrectomy patients.

Post-gastrectomy, changes in gastrointestinal and gastric endocrine functions7) can frequently lead to a reduction in food intake, and many patients have insufficient nutrient intake below the recommended dietary allowance for long periods8). Long-term malnutrition reduces muscle protein synthesis and increases muscle breakdown, resulting in muscle mass loss. Resistance exercise is crucial for stimulating muscle protein metabolism. Previous studies demonstrated that resistance exercise enhances skeletal muscle protein synthesis reactions9) and suppresses skeletal muscle breakdown10) even under energy restriction conditions. These findings suggest that resistance exercise may prevent muscle mass loss in patients prone to low energy intake after gastrectomy.

Protein and essential amino acid intake increase muscle protein synthesis11). In particular, the branched-chain amino acid (BCAA) leucine potentiates muscle protein synthesis12). In post-gastrectomy patients, intravenous amino acid infusion modulates muscle protein metabolism13). However, the effect of oral amino acid supplementation on muscle protein metabolism is unclear. For postoperative gastric cancer patients with reduced gastric capacity, supplement intake may reduce food intake due to the feeling of fullness14). Therefore, post-gastrectomy patients require low-volume supplements with high muscle protein synthesis effects. Wilkinson et al. showed that 3 g of leucine-enriched essential amino acids (LEAA) stimulated muscle protein synthesis, equivalent to ingesting 20 g of whey protein15). This finding suggests that LEAA supplements may be beneficial for post-gastrectomy patients.

Furthermore, combining resistance exercise with protein or essential amino acid intake can promote muscle protein synthesis16). Takegaki et al. showed that the intake of 2.5 g of LEAA enhanced the resistance exercise's muscle protein synthesis effect17). Kim et al. showed that exercise training with 3 g of LEAA supplementation twice daily increased muscle mass in sarcopenic elderly18). In addition, even under low energy intake, muscle synthesis response is higher when resistance exercise is with protein intake than when resistance exercise is performed alone9). These findings suggest that resistance exercise with LEAA supplements might reduce muscle mass loss in post-gastrectomy patients prone to low energy intake; however, no studies have focused on post-gastrectomy patients. Therefore, this study determined whether resistance exercise with LEAA supplementation would prevent muscle mass loss and improve physical function in post-gastrectomy patients. We hypothesized that resistance exercise with LEAA supplementation would prevent muscle mass loss.

PARTICIPANTS AND METHODS

We conducted a single-center, open-label, randomized controlled pilot trial. We used the CONSORT guidelines to guide study design and implementation. The Ethics Committee of the Department of Rehabilitation Sciences, Health Sciences University of Hokkaido (approval number: 15R017019) and the Saiseikai Otaru Hospital Ethics Committee approved the study. This study was retrospectively registered in a public registry on August 16, 2023. (UMIN-CTR: UMIN000051925). We enrolled participants who underwent gastrectomy at the Saiseikai Otaru Hospital between September 2015 and July 2017. The eligibility criterion was gastrectomy for gastric cancer. This study did not establish eligibility criteria based on gender, surgical procedure, extent of resection, or chemotherapy. Exclusion criteria were (1) difficulty in performing exercises due to physical or severe cognitive dysfunction and (2) requirement for restriction of protein intake due to severe renal dysfunction. All participants provided written informed consent based on the Helsinki Declaration. An independent statistical consultant performed participant allocation using a computer-generated unequal randomization table. Research personnel who assessed outcomes were blinded to allocation.

The study protocol is shown in Fig. 1. The participants were divided into two groups: the intervention group and the control group. Six days from postoperative day 1 (POD1) to POD6, both groups received standard postoperative care (diet, medication, and mild physical activity). In addition to the standard postoperative care, the intervention group received resistance training for the lower limbs twice a day, three times a week, for 15 days from POD7 to POD21. The intervention group was also given a LEAA supplement twice daily for 15 days from POD7 to POD21. When resistance training was performed, a LEAA supplement was taken within 30 minutes after each resistance training. When resistance training was not performed, LEAA supplements were taken between meals. The control group continued to receive standard postoperative care from POD7 to POD21. Both groups were assessed for body weight, body composition, physical function, blood samples, and nutrient intake before surgery and on POD7, POD14, and POD22. QOL was evaluated for both groups before surgery and on POD22.

The resistance exercise program consisted of three exercises for the lower limbs: leg extension, calf raise, and hip abduction. The load intensity was set at 70% of the one-repetition maximum, and the number of repetitions was set at ten for three sets.

The LEAA supplement was Amino Care Jelly Leucine 40 (Ajinomoto Co., Tokyo, Japan). The nutritional composition of the supplement is displayed in Table 1. The total amino acid content was 3 g, which included 1.20 g of leucine, 0.32 g of isoleucine, and 0.33 g of valine. The leucine content accounted for 40% of the total amino acid content.

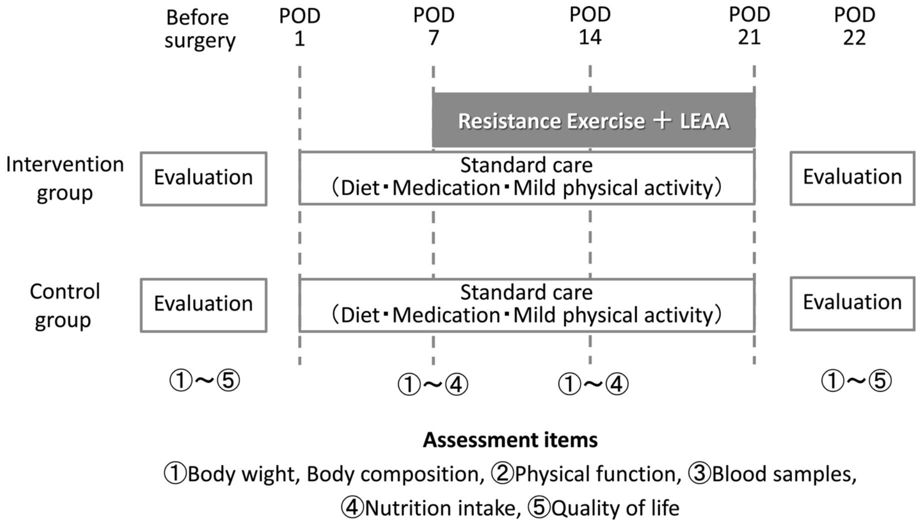

Fig. 1. Study overview.

Table 1. Nutrient composition of leucine-enriched essential amino acid (LEAA) supplement

Nutritional values (composition table, per 100 g)			Amino acid composition	
Calories	kcal	30	Leucine	1.20 g
Protein	g	3.0	Isoleucine	0.32 g
Fat	g	0	Valine	0.33 g
Carbohydrates	g	9.7	Lysine	0.50 g
Dietary fiber	g	-	Threonine	0.28 g
Water	g	87	Phenylalanine	0.20 g
Sodium	mg	75	Methionine	0.10 g
Salt equivalent	g	0.19	Histidine	0.05 g
Potassium	mg	5.1	Tryptophan	0.02 g
Phosphorus	mg	-	Total	3.00 g
VitaminD	IU	800		
VitaminB1	mg	0.2		
VitaminB6	mg	0.2		
VitaminB12	μg	0.4		

Body weight was measured in the morning using a digital scale (HD-661, Tanita Co., Tokyo, Japan). Body composition was measured in the morning while the participant was awake in a rested supine position while fasting using a body composition analyzer (InBody S10, InBody Japan Co., Tokyo, Japan) based on the bioelectrical impedance analysis method. The skeletal muscle index (SMI) was calculated by dividing the appendicular skeletal muscle mass by the square of the participants' height.

Physical function evaluation included assessment of lower extremity muscle strength and continuous walking distance. Isometric knee extension muscle strength was measured using a handheld dynamometer (μ-Tas F-1, Anima Co., Tokyo, Japan)[19]. The measured values were divided by the body weight to calculate the weight-bearing index (WBI). Continuous walking distance was measured using the six-minute walking test (6MWT) based on the American Thoracic Society guidelines[20]. Sarcopenia was diagnosed when low SMI and low muscle strength were present according to the Asian Working Group for Sarcopenia[21].

QOL was evaluated using the second version of the SF-36 health survey acute form (SF-36v2®). Data collection was conducted using a self-administered questionnaire following the SF-36v2® Japanese manual. The results were converted into scores ranging from 0 to 100 according to the SF-36v2® scoring manual.

Blood samples were collected in the early morning while fasting. Serum total protein, albumin, C-reactive protein, and creatinine were measured. In addition, an oral glucose tolerance test was performed before surgery and on postoperative day 21 to measure blood sugar, serum insulin, and C-peptide immunoreactivity.

Nutrient intake was calculated by combining meals, supplements, and parenteral nutrition. The average intake over three days, excluding the day before surgery, was measured for the preoperative period. For the postoperative period, we measured the average intake over three days, including the evaluation day and the preceding and following day. The dietary intake was calculated as the difference between the amount of food provided and the remaining amount. Intake of energy, protein, fat, and carbohydrates was measured. The physician and registered dietitian determined the food provided based on the total energy expenditure calculated using the Harris–Benedict equation and multiplied by the participants' activity and injury factors. The energy adequacy ratio was calculated by dividing the total energy expenditure by the energy intake.

Because this was a pilot study, a formal sample size calculation was not conducted. We estimated the number of participants required to be around 10% of the number required for the future definitive randomized controlled trial. Body weight, body composition, physical function, blood tests, and nutrient intake were analyzed using a mixed-effect model with repeated measures using a two-way analysis of variance. If a significant interaction effect was observed, we compared each level using Bonferroni's multiple comparison test. For the QOL evaluation, we used the Wilcoxon rank sum test. The comparison of the participants' primary characteristics between the groups was conducted using an unpaired t-test and χ^2 test. Statistical analysis was performed using IBM SPSS Statistics (version 26), with $p<0.05$ considered significant.

RESULTS

Figure 2 shows the flow of participants through the study. In all, 15 participants were screened for eligibility, of which one was excluded for difficulty performing exercises. The remaining 14 participants were randomly divided into two groups (six to the intervention group, and eight to the control group). Finally, five participants each were assigned to their respective groups. The overall dropout rate was 29%, and no significant difference was observed in the dropout rates between the two groups ($\chi^2(1)=0.73$, $p=0.58$). In the intervention group, there were no dropouts due to the exercise program or LEAA supplement.

Table 2 shows the participants' primary characteristics. The intervention group had significantly lower body mass index and body fat mass than the control group ($p<0.05$ for both). Both groups were similar in the other primary attributes.

Table 3 displays the changes in body weight, body composition, and physical functions. We failed to detect a significant difference in body wight, muscle mass, and fat mass between the groups. Body weight, muscle mass, and fat mass, were significantly lower at POD21 than at preoperative levels. ($p<0.01$, $p<0.05$, $p<0.05$, respectively). The percentage change in muscle mass at POD21 compared to preoperative values was −5.46 ± 1.50% in the intervention group and −6.56 ± 1.71% in the control group. In the intervention group, there was a significant improvement in WBI ($p<0.05$), while in the control group, no significant changes in WBI were observed. In the intervention group, WBI at POD21 was significantly higher than preoperative levels ($p<0.05$). WBI at POD14 and POD21were significantly higher than at POD7 ($p<0.05$ and $p<0.01$, respectively) in the intervention group. The changes in 6MWT did not differ between the groups. 6MWT was significantly higher at POD21 compared to at POD7 ($p<0.01$).

Table 4 displays the changes in QOL. In the items "physical function" and "mental health", the intervention group had significantly higher scores at POD21 than preoperatively ($p<0.05$ for both).

The changes in nutrient intake and blood test parameters did not differ between the groups.

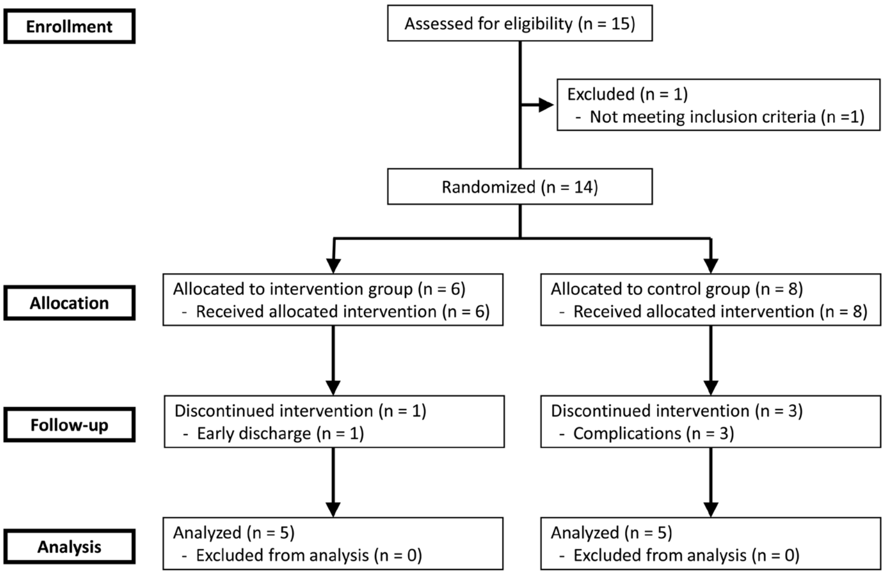

Fig. 2. Participant flow through the study.

Table 2. Participant characteristics

	Intervention group (n=5)	Control group (n=5)
Age (years)	68.6 ± 10.7	65.6 ± 19.6
Height (cm)	161.6 ± 7.8	161.2 ± 10.9
Weight (kg)	52.5 ± 9.6	59.6 ± 8.3
BMI (kg/cm^2)	19.9 ± 2.1*	22.9 ± 1.2
Muscle mass (kg)	41.3 ± 7.7	41.5 ± 10.8
Fat mass (kg)	8.8 ± 5.7*	16.2 ± 4.2
SMI (kg/m^2)	6.8 ± 1.2	6.3 ± 1.2
Grip strength (kg)	24.4 ± 6.5	20.4 ± 6.9
WBI (kgf/kg)	0.4 ± 0.1	0.4 ± 0.1
6MWT (m)	378.4 ± 55.2	333.2 ± 60.8
Gender		
Male	4	3
Female	1	2
Length of hospital stay (days)	26.4 ± 7.3	23.0 ± 5.2
Pathological classification		
1A-2B	3	2
3A-4	2	3
Surgical procedure		
Total gastrectomy	1	2
Distal gastrectomy	4	3
Cholecystectomy		
Yes	2	4
No	3	1
Reconstruction method		
R-Y	3	4
B-I	2	1
Postoperative chemotherapy		
Yes	1	1
No	4	4
Sarcopenia		
Yes	2	4
No	3	1

The two groups were compared using unpaired t-test and χ^2 test with Fisher's exact method for determining the significance. The results are presented as mean ± standard deviation. *$p<0.05$. R-Y: Roux-en-Y; B-I: Billroth I; BMI: body mass index; SMI: skeletal muscle index; WBI: weight bearing index; 6MWT: the six-minute walking test.

DISCUSSION

We examined the effects of resistance exercise with LEAA supplementation on muscle mass and physical functions during the first three weeks after gastrectomy for gastric cancer. We observed good adherence and participation rates, indicating that this program is feasible and acceptable to post-gastrectomy patients. We failed to detect a significant difference in muscle mass resulting from resistance exercise with LEAA supplementation. However, the intervention group showed a significant improvement in muscle strength and QOL. To our knowledge, this is the first interventional trial including resistance exercise with LEAA supplementation in post-gastrectomy patients.

The rate of muscle mass loss was 5.46% in the intervention group and 6.56% in the control group. Previous studies reported that the rate of muscle mass loss after gastrectomy for gastric cancer was approximately 5–10% one month after surgery[3, 22)]. The results of our study are similar to those of these studies, suggesting that resistance exercise with LEAA supplementation might not be effective in preventing muscle mass loss.

In the present study, protein intake after POD7 was approximately 1.1–1.2 g/kg in the intervention group, which met the recommended dietary allowance of 0.8 g/kg. Despite an adequate protein intake, the inability to prevent muscle mass loss

Table 3. Change in body weight, body composition, and physical function

		Preoperation	POD7	POD14	POD21	Group effect	Time effect	Group × Time effect
Body weight (kg)	Intervention group	52.5 ± 9.8	49.8 ± 9.5	49.6 ± 8.9	49.0 ± 8.7		**	
	Control group	59.6 ± 8.3	58.5 ± 8.1	56.3 ± 7.1	55.3 ± 7.2			
Muscle mass (kg)	Intervention group	41.3 ± 7.7	39.4 ± 6.8	39.3 ± 6.9	39.0 ± 7.4		*	
	Control group	40.9 ± 9.9	39.9 ± 10.7	38.7 ± 10.1	38.2 ± 9.4			
Fat mass (kg)	Intervention group	8.9 ± 5.7	8.3 ± 5.5	7.7 ± 5.3	7.9 ± 4.5	*	*	
	Control group	16.2 ± 4.2	15.7 ± 4.7	15.2 ± 4.4	14.7 ± 4.5			
WBI (kgf/kg)	Intervention group	0.39 ± 0.1	0.35 ± 0.2	$0.45 \pm 0.2^{*2}$	$0.47 \pm 0.2^{*1, **2}$		*	*
	Control group	0.38 ± 0.1	0.32 ± 0.1	0.35 ± 0.1	0.38 ± 0.1			
6MWT (m)	Intervention group	378.0 ± 55.2	328.0 ± 67.7	404.0 ± 35.9	407.0 ± 42.4		**	
	Control group	333.0 ± 60.8	235.0 ± 72.1	297.0 ± 53.1	343.0 ± 61.3			

We conducted a two-way analysis of variance using a mixed model and performed post-hoc multiple comparisons with Bonferroni's correction.
The results are presented as mean ± standard deviation. *p<0.05, **p<0.01, ^{*1}p<0.05 (vs. Preoperation), ^{*2}p<0.05 (vs. POD7), ^{**2}p<0.01 (vs. POD7),
WBI: weight bearing index; 6MWT: the 6-minute walking test.

Table 4. Change in quality of life (QOL)

		Preoperation	POD21
Role physical	Intervention group	25.0 (25.0–75.0)	81.3 (12.5–93.8)
	Control group	31.3 (25.0–71.9)	18.8 (0–40.7)
Physical functioning	Intervention group	70.0 (37.5–80.0)	90.0 (85.0–95.0)*
	Control group	75.0 (40.0–92.5)	85.0 (77.5–97.5)
Vitality	Intervention group	50.0 (28.1–62.5)	62.5 (53.1–84.4)
	Control group	81.3 (12.5–93.8)	62.5 (53.2–81.3)
Bodily pain	Intervention group	74.0 (11.0–90.0)	84.0 (47.5–100)
	Control group	100 (57.5–100)	84.0 (47.5–100)
General health perceptions	Intervention group	42.0 (27.5–64.5)	52.0 (44.5–62.0)
	Control group	40.0 (22.5–53.5)	57.0 (46.0–63.5)
Social functioning	Intervention group	50.0 (37.5–75.0)	88.0 (44.0–87.5)
	Control group	63.0 (44.0–100)	63.0 (44.0–94.0)
Role emotional	Intervention group	50.0 (29.5–100)	100 (41.5–100)
	Control group	33.0 (0–83.5)	25.0 (0–42.0)
Mental health	Intervention group	30.0 (15.0–60.0)	70.0 (50.0–85.0)*
	Control group	55.0 (27.5–87.5)	65.0 (60.0–87.5)

The Wilcoxson's signed rank test was used for the test. *p<0.05.
Results are presented as medians (interquartile range).

may be attributed to inadequate energy intake. Previous studies showed that the protein requirements for maintaining muscle mass increase under inadequate energy intake[23, 24]. In the present study, the energy intake after POD7 was significantly lower than the required energy intake, with an energy adequacy ratio of 70.6–82.9% in the intervention group. This might be a reason for the intervention group's inability to prevent muscle mass loss.

Changes in proteins' digestive and absorptive functions due to gastrectomy might influence muscle mass loss. Protein absorption transiently decreases due to small intestinal bacterial overgrowth after gastrectomy[25, 26]. In this study, 10% of the protein intake in the intervention group after POD7 was from amino acid supplements, and the remaining 90% was from dietary protein. Therefore, it is possible that an insufficient increase in blood amino acid concentrations due to protein digestive and absorptive disorders could have reduced muscle protein synthesis stimulation.

Previous studies reported that systemic inflammation decreases muscle synthesis reactions due to inhibition of amino acid absorption in the small intestine[27], restriction of the movement of BCAAs to muscles[27], increased oxidation of BCAAs[28], and enhancement of leucine resistance[29]. In addition, systemic inflammation excessively activates the proteolytic system in skeletal muscle, reducing skeletal muscle mass in cancer patients[30]. In the present study, the intervention group showed high C-reactive protein levels until POD21 after surgery. This chronic systemic inflammation may have affected a decrease in muscle mass.

WBI improved significantly in only the intervention group. This result is similar to recent systematic reviews on muscle strength under energy restriction31). The results of the present study suggest that even post-gastrectomy patients with low energy sufficiency rates could improve muscle strength through resistance exercise with LEAA supplementation.

The intervention group improved the “physical function” and “mental health” QOL scores. Singh et al. reported that in older adults, high-intensity exercise had a more significant effect on improving mood and QOL than low-intensity exercise32). Similarly, Katula et al. found that older adults who performed resistance exercise thrice a week for 12 weeks significantly improved QOL with high-intensity exercise than those who did not exercise33). The results of the present study suggest that high-intensity exercise may be more effective than standard care in improving psychological function and QOL.

The primary limitation of this study is that a small overall sample size may limit generalizability. Previous studies suggested that low body fat may affect muscle mass loss34). In our study, the intervention group had significantly lower preoperative body fat mass than the control group. However, we could not eliminate this factor because of the small sample size; therefore, the difference in preoperative body fat mass could impact intervention effects. Another limitation is that we did not measure blood amino acid concentrations; therefore, we could not examine the impact of protein digestion and absorption disorders caused by gastric resection.

We failed to detect a significant difference in whether resistance exercise with LEAA supplementation would prevent muscle mass loss in post-gastrectomy patients. However, resistance exercise with LEAA supplementation might be beneficial for muscle strength recovery and QOL improvement. Further studies are necessary, considering the impact of postoperative protein digestion and absorption disorders.

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Conflict of interest

The authors declare that they have no competing interests.

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