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A Randomized Controlled Trial on the Effects of Oral Collagen Treatment on the Medial Knee Joint Space and Functional Outcome among Veterans Memorial Medical Center Patients Diagnosed with Osteoarthritis of the Knee

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ABSTRACT

General Objective: To determine the effects of oral collagen treatment on the medial knee joint space and the functional outcome among patients diagnosed with osteoarthritis of the knee.
Specific Objectives: (a) To determine the effect of oral collagen treatment in improving the functional status of patients diagnosed with osteoarthritis of the knee using the Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis index, Likert scale version; (b) to determine the effect of oral collagen treatment in the knee joint space of patients diagnosed with osteoarthritis of the knee viewed and measured radiographically; and, (c) to compare the effect of oral collagen treatment with the standard treatment using non-streoidal anti-inflammatory drug (NSAID) as to WOMAC knee osteoarthritis index and medial knee joint space.
Study Design: Experimental, randomized, single-blind observer, open-labeled, controlled trial.
Setting: Government hospital, out-patient setting.
Patients: One hundred and fifty patients diagnosed with knee osteoarthritis were randomized into two groups. A sample of 113 patients completed the study. Fifty-five patients were in Group A while 58 patients were in Group B.
Methods/Interventions: Eligible subjects were randomly assigned to Group A who received oral collagen hydrolysate, 400 mg/capsule 3 capsules once a day at bedtime, or to Group B who underwent the conventional treatment of non-steroidal anti-inflammatory drug in the form of aceclofenac 100 mg/tablet 1 tablet twice a day for five days then as needed for pain. Both groups were also prescribed with topical analgesic in the form of ketoprofen gel to be applied twice a day as needed for pain, and physical therapy treatment thrice a week for two weeks. Follow up evaluation was done every month to assess developments from the symptoms. Initial radiograph of the knee was done prior to the intake of the medications and repeated after six months of completion of the intervention.
Main Outcome Measurements: Symptoms of knee osteoarthritis were evaluated using the WOMAC knee osteoarthritis index, Likert scale done every month for six months. Radiographs of the knee were obtained and measurement of the medial compartment of the tibiofemoral joint was done using a standard ruler in millimeters at the start of the study and after six months.
Results: Patients in Group A significantly scored lower in the average WOMAC score from baseline to the sixth month follow up. On the other hand, patients in Group B had no significant change in their average WOMAC score after six months. There was no significant difference in the medial knee joint space measured at baseline and after six months in both groups.
Conclusion: The administration of 1,200 milligrams of collagen hydrolysate daily for a period of six months has a beneficial impact on pain symptoms and joint function in patients with osteoarthritis.

Key Words: *Osteoarthritis, collagen hydrolysate, cartilage*

Group A were given **Genacol AminoLock® Collagen** product. See on page 5 where it is mentionned that Genacol was given to Group A

STATEMENT OF THE PROBLEM

Osteoarthritis is a degenerative joint disease characterized by progressive destruction of joint cartilage and associated structures such as bone, synovial and fibrous joint capsule and the periarticular musculature.[1] It is the most common of the rheumatic diseases and presents as a most disabling musculoskeletal disorder. It is likely to be a frequent problem for physiatrists who have outpatient musculoskeletal practices. The disease accounts for 25% of visits to primary care physicians.[2] Approximately 2.6 million adult Filipinos have arthritis.[3] Epidemiologic surveys estimate that 37% of adults have some radiographic evidence of osteoarthritis, with at least one fourth of those having moderate or severe disease.[4] Osteoarthritis causes pain, depression, anxiety, feelings of helplessness, limits activities of daily living and productivity, leads to disability, loss of everyday family joys and responsibilities. Because of these impairments, osteoarthritis-related disability creates huge costs for individuals, their families, and the nation. The impact on disability attributable to knee osteoarthritis is similar to that due to cardiovascular disease and greater than that caused by any other medical condition in the elderly.[5] Although younger adults develop osteoarthritis secondarily from injury and loss of biomechanical integrity, osteoarthritis most often occurs in the aging adult. The incidence and prevalence increased 2- to 10-fold from 30-65 years of age, and it increased further beyond 65 years.[6] It is projected that the number of people with arthritis will further increase due to longer life expectancy. The causes are multifactorial and the risk factors differ for every joint. Although any synovial joint can be affected, osteoarthritis occurs most frequently in the knee, hip, hand, and spinal apophyseal joints. There is increasing acknowledgment that osteoarthritis, particularly in the knee, can be regarded as a whole-organ degenerative process,[7] with an emphasis on the contribution of multiple articular and periarticular abnormalities in the clinical expression of the disease.

The impact of osteoarthritis is cause for concern. There is a need for an effective treatment for the millions of people with osteoarthritis. Currently, there is no cure for osteoarthritis. Management of the disease is focused on reducing pain, maintaining mobility, and minimizing disability with the use of nonspecific symptomatic agents like non-steroidal anti-inflammatory drugs (NSAIDs) which have been shown to negatively affect the progression of osteoarthritis in terms of joint structure changes. In addition, these NSAIDs have various adverse reactions like gastrointestinal complications, and can have various drug interactions with the other medications taken by most of the elderly patients. Left with no other choice, more and more patients are turning to alternative medicine for more natural treatments.

BACKGROUND

The articular cartilage is comprised of chondrocytes and an extracellular matrix which is maintained by the chondrocytes. The macromolecular framework of articular cartilage consists of collagens (predominantly type II collagen), proteoglycans, and non-collagenous proteins. This matrix provides the cartilage with its tensile stiffness and strength. The proteoglycans create the osmotic swelling pressure that is responsible for compressibility and elasticity of cartilage counteracted by the resistance of the intact collagen fibrils. Collagens contribute about 60% to the dry weight of the cartilage while proteoglycans provide 25-35%, and non-collagenous proteins and glycoproteins contribute 15-20%.[8] The disruption of the structural integrity of articular cartilage, its deterioration, and its eventual loss are a result of an imbalance between anabolic and catabolic activity in the cartilage tissue. The most common origins of this imbalance include chondrocyte senescence and pathophysiologic conditions such as osteoarthritis.

Most investigators feel that the primary change in osteoarthritis begins in the cartilage. There is an apparent change in the arrangement and size in the collagen fibers. The biomechanical data are consistent with the presence of a defect in the collagen network of the cartilage, perhaps due to disruption of the "glue" that binds adjacent fibers together in the matrix. It has been theorized that new treatments should focus on improving the health of this existing joint collagen. Several investigators have suggested that some substances may be capable of repairing damaged articular cartilage or at least deccelerate its progressive degradation.[9] Collagen hydrolysate, a natural component of gelatin, has been suggested as a mode of treatment. Since it contains abundant amino acids that play a role in the synthesis of collagen, it may possibly help maintain joint health.

At present, there is no single drug that results in reversal or prevention of osteoarthritic changes. Pain relief is the main goal of the medications of patients with osteoarthritis. Non-steroidal anti-inflammatory drugs are suitable for pain relief but response may not be outstanding and adverse effects should be considered. Depot glucocorticoids can have a pain-reducing effect over a number of weeks if given by intra- or periarticular injection. In animal experiments however it was shown that glucocorticoids can attack

joint cartilage; thus, it can only be given at most two to three times a year to the same joint. Topical anti-inflammatory drugs have no effect on osteoarthritis itself; however, there are indications that it is effective in relieving pain due to inflammation. Physiotherapy is an important aspect in the complex treatment of osteoarthritis. It focuses on function and postural training, range of motion and strengthening exercises, and application of heat or cold for pain relief.

Experiments with bovine cartilage cell cultures showed that collagen hydrolysate significantly increases the biosynthesis of type II collagen in articular chondrocytes. Treatment of cultured chondrocytes with 0.5mg/ml collagen hydrolysate over a culture period of 11 days induced a statistically significant, dose-dependent increase in type II collagen synthesis of the chondrocytes compared with untreated control cells ($p<0.01$).[10] In addition, the amount of proteoglycans has been shown to significantly increase after collagen hydrolysate administration ($p<0.05$).[11]

The primary imaging modality for the evaluation of osteoarthritis has been radiography. At best, joint space narrowing that is determined radiographically is an indirect measure of articular cartilage status. In experiments with radio-labeled collagen hydrolysate, it has been shown that a significant amount of collagen hydrolysate-derived peptides reach cartilage tissue within 12 hours after administration compared with control animals ($p<0.05$).[12]

The clinical benefits of collagen hydrolysate have been investigated in four open-label and three double-blind studies.[13] In 1979, results were published demonstrating the clinical effect of collagen hydrolysate on degenerative joint disease in patients with knee osteoarthritis. Patients received collagen hydrolysate orally for 1-6 months. The author reported results on 56 patients where 68% reported 'very good success' to 'noticeable improvement'[14] In a multi-national study, the effectiveness of pharmaceutical grade collagen hydrolysate (PCH) in decreasing osteoarthritis pain was evaluated in a randomized, double-blind placebo-controlled trial involving 389 patients. Results revealed that there was a meaningful statistically significant treatment advantage of PCH over placebo for pain and physical function. The effect of collagen hydrolysate on pain from osteoarthritis was also studied in a prospective, randomized, double-blind, placebo-controlled clinical trial, and the authors found that 81% of patients taking collagen hydrolysate achieved meaningful pain reduction, and 69% had a ± 50% decrease in consumption of analgesics.[15] In a multi-center study on 359 patients suffering from arthritis, substantial pain relief was achieved after administration of a mixture of L-cysteine and gelatin over a period of six months. Clinical studies have shown that a period of at least three to six months duration of daily intake of oral collagen hydrolysate is effective in relieving pain and improving physical function.

Based on the findings that collagen hydrolysate is absorbed from the intestine in its high molecular form, preferentially accumulates in cartilage, and is able to stimulate chondrocyte metabolism, it might be reasonable to use collagen hydrolysate as a nutritional supplement to activate collagen biosynthesis in chondrocytes in humans, especially under conditions where cartilage is under considerable stress. Collagen products are recognized as safe components of pharmaceuticals and foods by the US Food and Drug Administration (FDA) Center for Food Safety and Nutrition[16] and was designated as "Generally Recognized As Safe" (GRAS).

SIGNIFICANCE OF THE STUDY

Chondroprotection, the prevention of additional cartilage tissue loss, is perhaps the most likely future direction of osteoarthritis research and subsequent treatment. Collagen hydrolysate administration could be of potential merit for use in individuals such as the aged population at risk for development of joint degeneration. The high safety profile of collagen hydrolysate would make it especially attractive as a nutritional supplement for use over many years in such individuals in the prophylaxis of joint degeneration, as well as an agent with potential for therapeutic benefit in the active treatment of osteoarthritis. Future emphasis will likely be placed on both earlier diagnosis and treatment in the form of chondroprotection, rather than just analgesia. Given the importance of collagen to joint-related connective tissues, experimental data which support nutritional advantages to the use of collagen hydrolysate as a source of structurally important amino acids, and clinical trials that have been performed to assess the efficacy of collagen hydrolysate in the maintenance of normal articular structure, prevention of joint breakdown/dysfunction, and relief of symptoms related to osteoarthritis, the investigators conducted this drug trial to further study the effectivity of this medication. Investigation on the improvement of an osteoarthritic knee joint could further prove its worth. In addition, comparing its ability to relieve symptoms versus the standard treatment of using analgesics could prove better drug tolerability with less adverse effects. Clearly, natural remedies without side effects will enjoy a major opportunity in the joint pain market either in place of, or in addition to, these prescription alternatives if

proven effective. This option can reduce the financial burden of these patients as well as improve their quality of life. As of the writing of this paper, no similar study of this kind was previously conducted to the knowledge of the investigators.

OBJECTIVES

General Objective

To determine the effects of oral collagen treatment on the medial knee joint space and the functional outcome among patients diagnosed with osteoarthritis of the knee.

Specific Objectives

(a) To determine the effect of oral collagen treatment in improving the functional status of patients diagnosed with osteoarthritis of the knee using the Western Ontario and McMaster Universities (WOMAC) knee osteoarthritis index, Likert scale version.
(b) To determine the effect of oral collagen treatment in the knee joint space of patients diagnosed with osteoarthritis of the knee viewed and measured radiographically.
(c) To compare the effect of oral collagen treatment with the standard treatment using NSAID as to WOMAC knee osteoarthritis index and medial knee joint space.

METHODOLOGY

Study Design

Experimental, randomized, single blind observer, open-labeled, controlled trial.

Setting

Out-patient Department of a government hospital (Veterans Memorial Medical Center).

Selection of Subjects

One hundred and ten subjects were needed in this study to reject the null hypothesis that the response difference in the two groups is zero with a probability (power) of 0.8. Allowing for patient drop-outs, non-compliance to treatment and loss of test power due to non-parametric data analysis, a boosted sample of 75 patients per group was recommended.

Inclusion Criteria

- Male and female patients aged 50-80 years old diagnosed with primary osteoarthritis of the knee defined by the American College of Rheumatology (ACR) criteria with Kellgren and Lawrence grade of at least 2 and above.[17]
- Medically stable (no fluctuating blood pressure, no active systemic infection).
- Good cognitive function.
- Willing to participate in the study.

Exclusion Criteria

- Subjects who had taken any form of supplements or adjuvant therapy that may be indicated for the treatment of osteoarthritis like glucosamine sulfate, chondroitin sulfate, collagen, sodium hyaluronate, systemic or intra-articular corticosteroid therapy, and others that affect joint metabolism.
- Subjects with secondary osteoarthritis.
- Obese patients [body mass index (BMI) greater than 27 calculated as weight in pounds divided by the square of height in inches times 703].
- Patients with active peptic ulcer disease or gastrointestinal bleeding.

Examination and Treatment Assignment

The patients recruited underwent the usual medical consultation from the Out-patient Department. The physician filled up a standardized history and physical examination form for each patient to determine the patient's eligibility in the study. All possible participants had an initial x-ray of the knee, anteroposterior view, in a weight bearing extended position to determine the Kellgren and Lawrence radiographic stage. Once eligible, the patient was invited to participate in the study and a written consent form was signed. Each subject was randomly assigned to Group A, which is the test group, or Group B, which is the control group. A list of random code that was auto-generated was given to qualified patients. They were assigned to the treatment groups corresponding to the given random code.

Group A subjects were given the oral collagen supplement (Genacol®) 400mg/capsule, 3 capsules daily at bedtime for 6 months, and a topical analgesic needed for knee pain. Group B, the control group, received the standard treatment using an oral non-steroidal inflammatory drug, in the form of aceclofenac 100mg/tablet, 1 tablet twice a day for 5 days initially then as needed for pain, and topical analgesic (ketoprofen gel) to be applied twice a day as needed for pain. Both groups

underwent physical therapy three times a week for two weeks. Heating modalities, range of motion exercises, and muscle strengthening exercises were administered on each therapy session. Follow up evaluation was done every month. On the sixth month of follow up, repeat radiographic evaluation of the involved knee was done to determine if there were any changes in the knee joint. Compliance to the study medication was determined by asking the patient on their missed doses and by counting the remaining unconsumed capsules.

Main Outcome Measurements

Symptoms of osteoarthritis were assessed using the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index,[18] a validated and disease-specific questionnaire separately addressing severity of joint pain (5 questions), stiffness (2 questions), and limitation of physical function (17 questions) in the 48 hours before assessment.

The Likert Version of WOMAC is rated on an ordinal scale of 0 to 4 with lower scores indicating lower levels of symptoms or physical disability. Each subscale is summated to a maximum score of 20, 8, and 68, respectively. There is also an index score or global score, which is most commonly calculated by summating the scores for the 3 subscales.[19] The questionnaire is self administered and takes 5 to 10 minutes to complete.

The primary outcome measure for joint structural changes was represented by the mean joint space width of the medial compartment of the tibiofemoral joint. Weight bearing, anteroposterior radiographs of each knee were taken at baseline and at 6 months.

The patients stood bare-foot with their knees extended and their feet slightly internally rotated (~15Ú) and the posterior aspect of the knee in contact with the vertical cassette. The feet were positioned about 4 inches apart. The x-ray beam was centered about 1.5 inches inferior to the apex of the patella and perpendicular to the tibial plateau. The focus to film distance was approximately six feet. Using a standard ruler in millimeters, one experienced radiologist who was blinded as to the treatment of each subject measured the narrowest medial compartment of the tibiofemoral joint of each radiographed knee done at the start of the study. Measurement was repeated after the second x-ray done on the sixth month follow up. Results were compared and tabulated for analysis.

STATISTICAL ANALYSIS

Sample size was calculated on the basis of the recommendations available at the time of the study planning, of a 0.5 mm assumed difference in joint-space narrowing between the two groups. A sample size of at least 55 pairs of subjects was needed to be able to reject the null hypothesis that this response difference was zero with probability of (power) 0.8. The type I error probability associated with the test of this null hypothesis was 0.05. Allowing for patient drop outs, non-compliance to treatment and loss of test power due to non-parametric data analysis, a boosted sample of 75 patients per group was used.

Data was presented as mean ± SD or frequency and percent distribution whichever was applicable. Chi square test was performed to indicate any significant difference in the distribution of male and female patients between the two groups while t-test was performed to check for any significant difference in characteristics that were continuous variables. Paired sample t-test was used to compare the significance in change in values (WOMAC and medial knee joint space) of the two groups from baseline to the sixth month follow up. A p-value of < 0.050 was considered significant.

RESULTS

Sample Baseline Characteristics

Of the 150 subjects enrolled and randomly assigned to the groups, 113 patients were able to finish the study. Thirty-seven of them were either lost to follow up or dropped out of the study. Fifty-five patients were in Group A while 58 patients were in Group B. Patients in Group A were mostly female (70.9%), with an average age of 68 years old. The average BMI was 24. Average baseline WOMAC Score was 3 (severe), average baseline Kellgren-Lawrence score was 3 (moderate) and average baseline median knee-joint space was 4 mm. Patients given drug B were also mostly female (67.2%), with average age of 69 years old. The average BMI was 24. Average baseline WOMAC Score was 3 (severe), average baseline Kellgren-Lawrence score was 3 (moderate) and average baseline median knee-joint space was 4 mm.

Table 1 shows that the baseline characteristics and demographics of both groups are homogenous. Table 2 shows that the average Global WOMAC Scores improved from baseline to each follow-up among patients from both groups.

No significant difference was found between the two groups in terms of average WOMAC Scores at each follow up.

Table 1. Baseline Characteristics: Distibution of Sex, Average Age, Height, Weight, BMI and Baseline scores

Total No. of Patients	Group A 55		Group B 58		*p-value*
	No.	**%**	**No.**	**%**	
Male	16	29.1	19	32.8	*0.48*
Female	39	70.9	39	67.2	
	Mean	***SD***	***Mean***	***SD***	
Age	68	8.4	69	7.8	*0.13*
Height (in)	64	2.9	63	3.0	*0.41*
Weight (lbs)	139	18.6	138	14.5	*0.33*
BMI	24	2.0	24	1.5	*0.49*
Baseline WOMAC Score	3	0.7	3	0.7	*0.47*
Baseline Kellgren-Lawrence Score	3	0.7	3	0.7	*0.48*
Baseline Median Knee-Joint Space (mm)	4	2.2	4	1.7	

Treatment Response

Table 2. WOMAC Scores from Baseline to Sixth Follow-up

Total No. of Patients	Group A 55		Group B 58		*p-value*
WOMAC Scores	**Mean**	**SD**	**Mean**	**SD**	
Baseline	2.83	0.7	2.91	0.7	0.47
1st ff-up	2.38	0.6	2 59	0.7	0.42
2nd ff-up	2.04	0.8	2.42	0.8	0.35
3rd ff-up	1.65	0.7	2.29	0.8	0.25
4th ff-up	1.30	0.8	2.26	0.9	0.16
5th ff-up	1.05	0.9	2.17	0.9	0.14
6th ff-up	0.76	0.9	1.87	1.2	0.11

Figure 1 shows the decreasing trend of the average WOMAC Scores of both groups; however, Group A had a lower WOMAC Score at the sixth follow as compared to Group B.

Figure 1. Graphical Representation of the WOMAC Scores

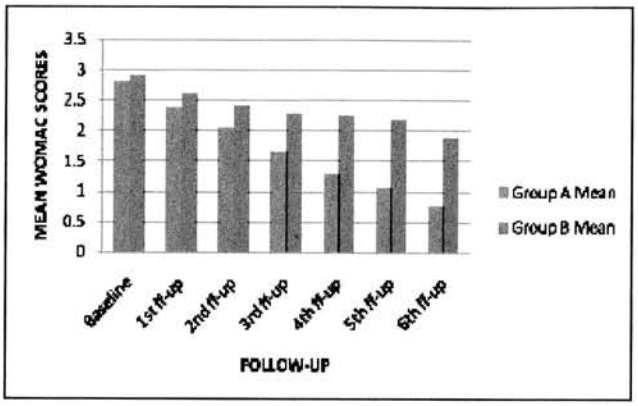

Table 3 shows that there was a significant drop in the average Global WOMAC Scores among patients in Group A from baseline to the sixth follow up compared with the other group where the drop in the WOMAC score was not statistically significant.

Table 3. Comparison of Global WOMAC Scores of Baseline to Sixth Follow-up

	Group A		Group B	
	t-stat	*p-value*	*t-stat*	*p-value*
WOMAC 1st-Baseline	0.5	0.33	0.3	0.37
WOMAC 2nd-Baseline	0.7	0.23	0.2	0.32
WOMAC 3rd-Baseline	1.1	0.13	0.1	0.29
WOMAC 4th-Baseline	1.4	0.08	0.1	0.29
WOMAC 5th-Baseline	1.5	0.07	0.1	0.26
WOMAC 6th-Baseline	1.8	0.04	0.0	0.21
WOMAC 1st-Baseline	0.5	0.33	0.3	0.37
WOMAC 2nd -1st	0.3	0.38	0.4	0.44
WOMAC 3rd -2nd	0.4	0.34	0.3	0.45
WOMAC 4th -3rd	0.3	0.37	0.4	0.49
WOMAC 5th - 4th	0.2	0.41	0.4	0.46
WOMAC 6th - 5th	0.3	0.38	0.4	0.40

Table 4 shows that among Group A patients, the average medial knee joint space widened from 4.2 mm at baseline to 4.4 mm at sixth follow up. On the other hand, the medial knee joint space among Group B patients narrowed from 4.3 mm to 3.8 mm. However, the difference was not statistically significant.

Table 4. Median Knee Joint Space at Baseline and Sixth Follow-up

	Group A		Group B		
Total No. of Patients	55		58		
	Mean	***SD***	***Mean***	***SD***	***p-value***
Median Knee Joint Space (mm)					
Baseline	4.2	2.2	4.3	1.7	0.45
6th ff-up	4.4	2.0	3.8	1.8	0.31
		p-value			***p-value***
Knee Joint Space 6th - Baseline		0.42			0.32

DISCUSSION

The clinical data collected in this study further confirms existing clinical data that show the positive influence of collagen hydrolysate on joint symptoms as well as improving the functional status in patients diagnosed with osteoarthritis. However, its effectiveness was significantly seen only after six months of administration of the said medication as compared to that of the control group which showed no significant difference when comparing the baseline with the sixth follow up results. The longer time for this medication to take effect could be attributable to the smaller amount of dosage used in this study which was 1.2 grams of collagen hydrolysate daily, as compared to previous studies which used 10 grams daily and a significant difference in the joint symptoms was already seen at about six to eight weeks time. The clinical improvement in symptoms may be explained by the direct impact collagen hydrolysate has on the joint cartilage. It has the potential to rebuild some of the cartilage that may be lost during the osteoarthritic process by the stimulation of chondrocytes and the increased synthesis of extracellular matrix.

Structurally, this study did not show any significant change in the medial knee joint space of an osteoarthritic knee, however, there was note of increase in the average medial knee joint space between sixth follow up and baseline. Continuous administration of collagen hydrolysate for a longer period of time could possibly elicit a significant amount of improvement.

CONCLUSION

The administration of 1,200 milligrams of collagen hydrolysate daily for a period of six months has a beneficial impact on pain symptoms and joint function in patients with osteoarthritis. Significant improvement was seen in the WOMAC Score on the sixth month of intake of the said medication as çompared to the intake of non-steroidal anti-inflammatory drugs. Structurally, however, there was no statistically significant improvement in the medial knee joint space of patients with osteoarthritis after six months in the intake of either medication.

RECOMMENDATION

The investigators of this study recommend extending the duration of the observation period in the intake of collagen hydrolysate to further study its effectivity in improving the medial knee joint space of an osteoarthritic knee.

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