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# The Effect of Apatite Carbonate Membrane Application on Periodontal Tissue after Scaling and Root Planing Treatment

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Abstract : The aim of this study was to evaluate the effect of adjunctive apatite carbonate membrane on pocket depth and clinical attachment loss in chronic periodontitis. The research method was a randomized control trial, double-blind, and split mouth, the examination carried out before and after the treatment. Parameters examined including pocket depth and clinical attachment loss. The study samples were chronic periodontitis patients that came to Periodontics Clinic of Faculty of Dentistry Padjadjaran University Dental Hospital, consisted of 11 male and 11 female patients with the mean of ageof 48,6-years. All patients were treated withscalingand root planing followed by the application of apatite carbonate membrane in the deepest pockets of selected teeth, then covered by periodontal pack. Clinical examination was also carried outon the 30<sup>th</sup> day. Data analysis was tested by Wilcoxon test. The results from the clinical examination of the gingiva before treatment (H<sub>0</sub>) were as follows: the mean of pocket depth on both treatment and control group was 6 mm; the clinical attachment loss on both treatment and control group was 7 mm. The results from clinical examination after treatment  $(D_{30})$  were as follows: the mean of pocket depth on both treatment and control group was 3 mm; the clinical attachment loss on treatment group was 4.5 mm and on control group was 4 mm. The difference mean of pocket depth (PD) and attachment loss (AL) at  $D_0$  compared to  $D_{30}$  was significant (p<0.001). Conclusion: Apatite carbonate membrane as an adjunctive therapy after scaling and root planing had significant effects on pocket depth and clinical attachment loss resulted in the PD and CAL reduction in chronic periodontitis.

## Introduction

Periodontitis is a periodontal tissue disease caused by disruption of the homeostatic process of subgingival plaque bacteria.<sup>Darveau,2010</sup> Periodontitis causes periodontal tissue destruction including loss of periodontal pocket connective tissue attachment and alveolar bone destruction, resulting in tooth loss, soreness, and mastication disorder.<sup>Pilhstrom BL,2005</sup>

The initial treatment of chronic periodontitis is scaling and root planing with the main purpose of the treatment is to create and maintain healthy periodontal tissue. Adjunctive therapy to optimize periodontal tissue

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healing after scaling and root planing is a local therapy on periodontal pocket through the use of periodontal chip. Azmak N,2002

Periodontal chip was discovered in 1998 and having biodegradable properties. Periodontal chip persisted in the pocket for 7-10 days and able to restore the attachment loss and reduce the pocket depth. The most well-known periodontal chip is the chlorhexidine chip. The use of periodontal chip-like materials was under development at present, which was with apatite carbonate material combined with gelatin. This material referred as the apatite carbonate membrane.<sup>Bade HI,2010; Rabbani GM,1981</sup>

Indicators of successful periodontitis treatment can be detected through a clinical examination of pocket depth, BOP, and clinical attachment loss level.

Periodontitis is a multifactorial disease affecting the tissues surrounding the teethcaused by the microbial biofilm layer (dental plaque). Periodontitis always begins with the occurrence of gingivitis, but not every gingivitis becomes periodontitis. Clinical features that distinguish periodontitis from gingivitis is the presence of clinical attachment loss.<sup>Loos BG,2005; Rateitschak KH,2006</sup>

The quantity and virulence of microorganisms, as well as host body defense factors (immunity, genetics, hereditary and risk factors) determine the initiation and development of periodontal tissue destruction. Rateitschak KH,2006

Accumulation of plaque bacteria is the initial factor of periodontitis and also the risk factors that may increase the severity and development of periodontitis as a systemic disease, besides another factor such as age, smoking, stress, and genetic.<sup>Rateitschak KH,2006</sup>

The most common periodontitis is chronic periodontitis, with the prevalence rate of 95. Chronic periodontitis defined as an inflammatory disease in the tissues surrounding the teeth involves the progressive loss of attachment and alveolar bone. This definition marks the main clinical features and etiological characteristics of chronic periodontitis which are the formation of microbial plaques, inflammation of the periodontal tissues, attachment loss, and alveolar bone destruction.<sup>Rateitschak KH,2006</sup>



Figure 1. Clinical feature of chronic periodontitis<sup>11</sup>

Chronic periodontitis generally does not cause any soreness, thus makes the patient does not aware of any abnormalities in the oral cavity. The impact of this ignorance leads to a lack of motivation to get any initial treatment.<sup>Novak JM,2006;Rateitschak KH,2006; Lindhe J,2013</sup>

Chronic periodontitis can be diagnosed clinically, then supported by radiographic examination of alveolar bone loss. Clinical characteristics of chronic periodontitis include the accumulation of supragingival and subgingival plaques commonly associated with calculus formation, gingival inflammation, pocket formation, and progressive loss of periodontal attachment and alveolar bone.

The severity of periodontitis commonly related to time. Along with an individual aging, the progressive loss of attachment and alveolar bone occur more and getting worse due to the accumulated destruction. The severity of periodontitis classified into three categories: mild/slight, moderate, and severe.<sup>Rateitschak KH,2006</sup>

Effectivity of scaling and root planing may been hanced with adjunctive therapy including systemic and topical therapy. Systemic therapy has several disadvantages such as the low concentration on the tissue, the need for the certain time range, and only able to eliminate non-pathogenic bacteria. Topical application preparations include mouthwash. Mouthwashes cannot last long in the pocket and are unable to get into deep periodontal pockets, only 5% of the amount of mouthwash permeates into the periodontal pocket. Other preparations are gel and chlorhexidine chips applied to the periodontal pocket. The gel and chip dosage forms have a long-lasting advantage in the pocket and do not need to removed because they will disappear automatically.<sup>Rateitschak KH,2006</sup>

Apatite carbonate (CHA) is a form of apatite mineral  $(Ca_{10}F_2(PO_4)_6)$  in the form of tissue graft material with good compatibility and bioresorbability. <sup>Jokanovi V,2017</sup>Biologically, apatite is the part of enamel, dentin, and bone, and also stoichiometrically different with hydroxyapatite (HA), due to the fewer contents of carbonate ions. CHA has a substitution of  $CO_3^{2-}$  thus causing CHA to have better bioactivity solubility than hydroxyapatite. <sup>Rabbani GM,1981</sup>The n-CAP material with the formula of  $(Ca_{10}(PO_4)_{6-x}(CO_3)_x(OH)_2)$  suggested better biological activities compared to hydroxyapatite due to the incorporation of carbonate into hydroxyapatite which can increase its solubility, reduce crystallinity, alter crystalline form, and developing the chemical reactivity due to the weaker bonds.CHA is able to increase the local concentrations of calcium and phosphate ions that play an important role in bone formation. <sup>Anna ID, 2010</sup>

The chemical bond occurs between gelatin and apatite is the carboxylate bond in the two phases of the material.<sup>Kazemzadeh-Narbat M,2006</sup>The bonding occurs between the Ca<sup>2+</sup> ions in the apatite and the COO<sup>-</sup> cluster in gelatin.<sup>Chang MC,2003</sup>Research conducted by Sivakumar and Rao showed that the addition of HA having similar chemical structures with CHA thus gelatin is a carrier material in the drug delivery system (DDS) technology.<sup>Sivakumar M,2002</sup>

The addition of apatite to gelatin has been studied with several methods and concentrations. The results from a study conducted by Kim with the apatite composition of as much as 20%, 40%, and 60% in the gelatin membrane - HA revealed that the higher the apatite composition of gelatin, the fewer fibers incompatibility, followed by the finding of crystalline formation.

Apatite membranes, though synthetically processed, are still similar to biological apatites, with few distinguishers such as biological apatites formed in physiological conditions, whereas synthetic apatite membranes formed at high temperatures. Also, biological apatites rarely found in small sizes and fragments and only available in many composite forms with three-dimensional structures with the organic matrix. Whereas apatite membranes available in a purely inorganic two-dimensional structure. Another difference is that biological apatite contains very few crystalline and micro size, whereas the apatite membranes have better crystallization. <sup>Xu G,2001</sup>

The study conducted by Ardhani et al.in 2016on the use of apatite carbonate membranes suggested that the membrane acts as a metronidazole carrier system for periodontal disease, with capability of enhancing the cell proliferation and transportability of oxygen and nutrient.<sup>Ardhani R,2011</sup>

The study of Liao et al. in 2005 on the use of Guided Tissue Regeneration (GTR) membranes using the combination of various carriers with hydroxyapatite or nano carbonate active compounds were able to increase the adhesion and cell proliferation in periodontal ligaments for as much as 30%.<sup>Liao S,2005</sup>

Apatite carbonate membranes play a role in the healing process due to its biodegradable properties, ability to increase adhesion and cell proliferation in periodontal ligaments, facilitates oxygen transport and nutrient supply to the adjacent tissue.<sup>Liao S,2005; Xu G,2001</sup>

The purpose of this study was to determine the effect of apatite carbonate membrane application towards the healing process after scaling and root planing treatment in chronic periodontitis patients based on the pocket depth measurement and clinical attachment loss rate.

## Methods

The total sample was as much as 22 chronic periodontitis patients of the Periodontics Clinic of Faculty of Dentistry Padjadjaran University Dental Hospital, chosen with a randomized control trial method. The inclusion criteria were as follows: male and female with the age interval of 36-62 years; having periodontal pocket depth at least 5mm or deeper; willing to participate in the study by signing informed consent. The exclusion criteria were as follows: patients with systemic disease; smoker; patients with antibiotics, anti-inflammatory, and any mouthwashes usage; using dental prosthesis or orthodontic appliances.

Sample determinated by randomized control trial, double-blind, and split mouth. The study was conducted clinically then tested in the laboratory before and after treatment, to determine the level of pocket depth, and attachment loss. The materials used in this study were apatite carbonate membrane, rubber gloves, masks, pledgets, and sterilized cotton rolls and cotton pellets.

All patients fulfilled inclusion and exclusion criteria were informed about the detail of the study then signed the informed consent. The initial examination was performed involving the general data recording, medical history, and extraoral and intraoral examination including pocket depth and attachment loss, followed by scaling and root planing.

The application of apatite carbonate membrane into the periodontal pocket was carried out after scaling and root planing. Pocket depth and attachment loss measured before SRP and after day 30 after SRP.

## Results

The study samples were patient with chronic periodontitis came to the Periodontics Clinic of Faculty of Dentistry Padjadjaran University Dental Hospital, consisted of 11 male (50%) and 11 female (50%) patients with the mean of age was 48,6-years withage interval between 36-62 years. The education level consisted of elementary school 4 patients (18.2%), junior and senior high school 10 patients (45.5%), higher education 8 patients (36.6%). 17 patients were employed(77.3%), and 5 patients were unemployed(22.7%). The sample's characteristic was presented in **Table 1**.

Characteristic	Amount
Gender:	
Male	11
Female	11
Age (years):	
$_{\rm X}({\rm SD})$ : 48.6 (9.0)	
Interval: 36 – 62	
Education level:	
Elementary school	4
Junior and senior high school	10
Higher education	8
Employment status:	
Employed	17
Unemployed	5

#### Table 1.Sample's characteristic (n=22)

Gingival clinical examination, including pocket depth (PD) and attachment loss (AL) measurements, were recorded towards all subjects in the treatment and control group, followed by scaling and root planing. The apatite carbonate membranes was applicated on the treatment group. The gingiva was covered by the periodontal pack. Pocket depth and attachment loss level were recorded at base line (D0). At 1<sup>st</sup> week and day 30 (D30), the periodontal pack was removed.

	Variable	Group	Group		
		Treatment	Control		
I.	D0 data				
	a. PD	6**	6	0.813	
		(5 - 9)	(6 - 8)		
	b. AL	7	7	0.971	
		(6 - 10)	(5 - 10)		
II.	D30 data				
	a. PD	3	3	0.178	
		(2 - 8)	(2 - 8)		
	b. AL	4.5	4	0.157	
		(2 - 8)	(2 - 10)		
Co	mparison				
	a. PD				
		p < 0.001	p < 0.001		
	b. AL				
		p < 0.001	p < 0.001		

Table 2.Clinical comparison (PDand AL) of the treatment and control group

#### Notes: \*) based on the Wilcoxon test result\*\*) median and range value

Clinical examination of the patient's gingiva after treatment (D30): The mean of the pocket depth in both groups was 3 mm with interval2-8 mm; The attachment loss on the treatment group was 4.5 mm and on the control group was 4 mm, with interval 2-8 mm on the treatment group and 2-10 mm on the control group, as shown in **Table 2.** 

Based on the results presented in **Table 2**, the mean difference of pocket depth (PD) and attachment loss (AL) in D0 were significant with p<0.001. This result suggested that attachment loss (AL) was decreased significantly on the  $30^{\text{th}}$  day after treatment.

The mean difference of pocket depthon the treatment group was 2.6818 with the highest value was 4, and the lowest value was 0 (SD=1.24924). Whilethe mean difference of pocket depthon the control group was 3.3182 with the highest value was 6, and the smallest value was 0 (SD=1.28680). The mean of AL on the treatment group was 2.5000, with the highest value was 4, and the lowest value was 0 (SD=1.26303). Whilethe mean value of AL in the control group was 3.2273, with the highest value was 6, and the lowest value was 0 (SD=1.37778).

Table3. The mean difference of pocket depth(probing) and AL between D0 and D30 in the treatment and
control group

	Group	Ν	Mean	SD	Standard error of the mean	P-Value
Probing	Treatment	22	2.6818	1.24924	.26634	
	Control	22	3.3182	1.28680	.27435	0.63636
AL	Treatment	22	2.5000	1.26303	.26928	
	Control	22	3.2273	1.37778	.29374	0.72727

**Table3.** showed descriptive tables of mean and standard deviation of pocket depth, and AL difference between the treatment and control group. The mean difference of pocket depth on the treatment group was lower than the control group, similarly with the mean difference of the AL. This results suggested that mean difference between each groupwas changed from D0 to D30. Clinically, the difference of pocket depth and AL on the control group showed better result than the treatment group.

Based on the comparative test using independent t-test in **Table 3.**, the mean difference between before (D0) and after (D30) application of apatite carbonate membrane, pocket depth and AL between treatment group and control group showed no significant difference (p>0.05).

Based on the Mann-Whitney test of the pocket depth difference obtained the Z score of -1.253, with the p-value of 0.210. It might be stated that there was no difference on the pocket depth between the treatment and control group.

Based on the Mann-Whitney test of the AL difference obtained Z score 1.496, with the p-value 0.135. It might be stated that there was no difference in the AL between the treatment and control group.

## Discussion

The purpose of this study was to evaluated the effect of apatite carbonate membrane application towards the healing process after scaling and root planing treatment on chronic periodontitis patients. The clinical parameters including pocket depth, and attachment loss, were recorded, at the first visit after scaling and root planing treatment. The comparison was performed between the treatment and control group to the difference between adjunctive therapy with and without the apatite carbonate membrane.

Twenty two chronic periodontitis patients age group of 36-62 years fulfilled the inclusion criteria and excluded the exclusion criteria were examined in this study.

The apatite carbonate membrane is a synthetic product of a thin layer of gelatin containing apatite carbonate which now already produced in Gajah Mada University Indonesia. The apatite carbonate in membrane histologically known has a good biocompatibility and the consistency of the deposited carbonate increase gradually along with the increased solubility of the apatite collagen membrane.<sup>Novak JM,2006</sup>

The membrane is biodegradable and good biocompatibility, resembling the bone connective tissue collagen matrix, and alsoable to well-identified and well controlled to incise the increased attachment and cell spread.

The apatite carbonate membrane had proven of possessing a greater mechanical strength, more dense and stable, and also has an untilmate tensile strength on the normal range thus optimizing its application capability in the body, specifically ini this study is in the periodontal pocket. The consistency of the apatite carbonate membrane used in this study was 7:3 with consideration that at concentrations based on prior studies having numerous pores that increased cell proliferation and facilitated oxygen transport and nutrient supply to the adjacent tissue.<sup>Ana ID,2010; 33,34</sup>

The apatite carbonate membrane was expected to be able to reduce the depth of the periodontal pockets as well as the clinical attachment loss through its role in the periodontal tissue healing process, including the proliferation of fibroblasts as collagen connective tissue cells which were the main compounds in the formation of collagen fibers in periodontal ligament collagen.

The results showed that there was a significant improvement in the clinical parameters of the pocket depth and clinical attachment loss reduction on both treatment and control groups. This results might be influenced by various local factors, such as the ability and motivation of the patient in maintaining the oral hygiene, anatomical form of the radicular and the complexity of the periodontal pocket, and also the position and arrangement of teeth in the jaw that makes the plaque control was difficult to be carried out.

## Conclusion

The application of the apatite carbonate membrane as an adjunctive therapy after scaling and root planing to patient with chronic periodontitis could be effective in reducing pocket depth and clinical attachment loss.

## References

 Ana ID, Matsuya S, Ishikawa K. Engineering of Carbonate Apatite Bone Substitute on Composition – Transformation of Gypsum and Calcium Hydroxide. Engineering. May 2010;2: p. 344 – 352. DOI: 10.4236/eng.2010.25045.

- Ardhani R, Susilowati R, Ana ID. Fuctional Recovery of Sciatic Nerve on Application of Scaffold and Autologous Growth Factor : A Premilinary Study. Proceedings of Scientific Forum X – 2011 International Seminar and Dental Expo; 2011 October 6-8; Jakarta: Scientific Forum X – 2011 Committee; 2011.
- 3. Azmak N, Atilla G, Luoto H, Sorsa T. The Effect of Subgingival Controlled-Release Delivery of Chlorhexidine Chip on Clinical Parameters and Matrix Metalloproteinase-8 Levels in Gingival Crevicular Fluid. J Periodontol. 2002 Jun;73(6): p. 608-15. DOI: 10.1902/jop.2002.73.6.608.
- 4. Bader HI. Adjunctive Periodontal Therapy: A Review of Current Techniques. Dent Today. Jul 2010;29(7): p. 94-6, 98; quiz 98, 103.
- 5. Baum BJ, Yates JR 3rd, Srivastava S, Wong DT, Melvin JE. Scientific frontiers: emerging technologies for salivary diagnostics. Adv Dent Res. Oct 2011;23(4): p. 360-8. DOI: 10.1177/0022034511420433.
- 6. Bundela H, Bajpai AK. Designing of Hydroxyapatite-Gelatin Based Porous Matrix as Bone Substitute : Corelation with Biocompatibility Aspects. eXPRESS Polymer Letters. Feb 3, 2008;2(3):p. 201-13. DOI: 10.3144/expresspolymlett.2008.25.
- 7. Chang MC,Ko CC, Douglas WH. Preparation of Hydroxyapatite-Gelatin Nano Composite. Biomaterials. Aug 2003;24(17): p. 2853-62.
- 8. Darveau RP. Periodontitis a polymicrobial disruption of host homeostasis. Nat Rev Microbiol. Jul 2010;8(7): p. 481-90. DOI: 10.1038/nrmicro2337.
- 9. Jokanovi V, Nik I, Uskokovi D. Synthesis of Nano Structured Carbonated Calcium Hydroxyapatite by Ultrasonic Spray Pyrolysis. J Ceram Process Res. 2017;5(2): p. 157-162.
- 10. Kazemzadeh-Narbat M, Orang F, Solati-Hashjin M, Goudarzi A. Fabrication of Porous Hydroxyapatite-Gelatin Composite Scaffolds for Bone Tissue Engineering. Iran Biomed. Oct 2006;10(4): p. 215-23.
- 11. Kim YS, Kwon HK, Kim BI. Effect of Nano Carbonate Appatite to Prevent Re-Stain After Dental Bleaching in Vitro. JDent. Sep 2011;39(9): p. 636-42. DOI: 10.1016/j.jdent.2011.07.002.
- 12. Landi E, Tampieri A, Celotti G, Vichi L, Sandri M. Influence of Synthesis and Sintering Parameters of Carbonate Apatite. Biomaterials. May 2004;25(10): p. 1763-70.
- 13. Larivee J, Sodek J, Ferrier JM. Collagenase and collagenase inhibitor activities in crevicular fluid of patients receiving treatment for localized juvenile periodontitisJ Periodontal Res. Nov 1986;21(6): p. 702-15.
- Lee SY, Kwon HK, Kim BI. Effect of Dentine Tubule Occlusion by Dentifrice Containing Nano-Cabonate Apatite J Oral Rehabil. Nov 2008;35(11): p. 847-53. DOI: 10.1111/j.1365-2842.2008.01876.x.
- 15. Liao S, Wang W, Uo M, Ohkawa S, Akasaka T, Tamura K, et al. A Three Layered Nano-Carbonated Hydroxyapatite/ Collagen/ PLGA Composite Membrane for Guided Tissue Regeneration. Biomaterials. Dec 2005;26(36): p. 7564-71. DOI: 0.1016/j.biomaterials.2005.050.
- 16. Lindhe J, Lang NP, Karring T. Clinical Periodontology and Implant Dentistry. 5<sup>th</sup>ed. Hoboken:John Wiley & Sons; 2013.
- 17. Loos BG, Tjoa S. Host-derived diagnostic markers for periodontitis: do they exist in gingival crevice fluid?Periodontol 2000. 2005;39: p. 53-72. DOI: 10.1111/j.1600-0757.2005.00129.x.
- 18. Manson JD, Eley BM. Outline of Periodontics. 4<sup>th</sup> ed. London: Wright;2000.
- 19. Nikcevic I, Jokanovic V, Mitric M, Nedic Z, Makovec D, Uskokovic D.Mechanochemical synthesis of nanostructured fluorapatite/fluorhydroxyapatite and carbonated fluorapatite/fluorhydroxyapatite. J Sol State Chem. Jul 31, 2004;177(7): p. 2565-74. DOI: 10.1016/j.jssc.2004.03.024.
- 20. Novak JM, Novak KE. Smoking and Periodontal Disease.In: Newman MG, Takei HH, Klokkevold PR, Carranza FA. Carranza's Clinical Periodontology. 10<sup>th</sup> ed. Philadelphia: Saunders-Elsevier; 2006. p. 245-53.
- Pihlstrom BL, Michalowicz BS, Johnson NW. Periodontal diseases. Lancet. Nov 19, 2005;366(9499): p. 1809-20. DOI: 10.1016/S0140-6736(05)67728-8.
- 22. Rabbani GM, Ash MM Jr, Caffesse RG. The Effectiveness of Subgingival Scaling and Root Planing in Calculus Removal.J Periodontol. Mar 1981;52(3): p. 119-23. DOI: 10.1902/jop.1981.52.3.119.
- 23. Rateitschak KH, Rateitschak EM, Wolf HF, Hassel TM. Color atlas of periodontology. 1<sup>st</sup> ed. New York: Thieme Inc.; 1985.
- 24. Ren F, Ding Y, Leng Y. Infrared Spectroscopic Characterization of Carbonated Apatite : A Combined Experimental and Computational Study. J Biomed Mater Res A. Feb 2014;102(2): p. 496-505. DOI: 10.1002/jbm.a.34720.

- 25. Ryan ME, Ramamurthy S, Golub LM. Matrix metalloproteinases and their inhibition in periodontal treatment. Curr Opin Periodontol. 1996;3: p. 85-96.
- 26. Sivakumar M, Rao KP. Preparation, Characterization and In Vitro Release of Gentamycin from Caralline Hydroxyapatite-Gelatin Composite Microspheres. Biomaterials.Aug 2002;23(15): p. 3175-81. DOI: 10.1016/S0142-9612(02)00066-2.
- Susin C, Haas AN, Valle PM, Oppermann RV, Albandar JM. Prevalence and risk indicators for chronic periodontitis in adolescents and young adults in South Brazil. J Clin Periodontol. Apr 2011;38(4): p. 326–333. DOI: 10.1111/j.1600-051X.2011.01699.x.
- Taylor JJ. Protein Biomarkers of Periodontitis in Saliva. ISRN Inflammation. Apr 22, 2014;2014: p. 1-18. DOI: 10.1155/2014/593151.
- 29. Wang M. Composite Scaffolds for Bone Tissue Engineering. Am J Biochem & Biotech. 2006;2(2): p. 80-84.
- 30. Xu G, Aksay IA, Groves JT. Continous Crystalline Carbonate Apatite Films : A Biomimetic Approach. J Am Chem Soc. Mar 14, 2001;123(10):p. 2196-203.
- Young S, Wong M, Tabata Y, Mikos AG. Gelatin As A Delivery vehide for the Controlled Release of Bioactive Molecules. J Control Release. Dec 5, 2005;109(1-3): p. 256-74. DOI: 10.1016/j.jconrel.2005.09.023.

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