Oral Health Linked to Obstructive Coronary Heart Disease in Cross-Sectional Study

Corresponding Author:
Ali Jasim Muhamed, Department of Anesthesia Techniques, Hilla University College, Babylon, Iraq

ABSTRACT:
Background: Coronary artery disease (CAD) is a principal source of cardiovascular illness and death globally. Various risk factors contribute to an increased risk of CAD. Growing evidence proposes that inflammation may contribute in promoting acute thromboembolic events in susceptible individuals. Oral health, encompassing dental and periodontal health, is a significant public health concern affecting individuals throughout their lifespan. Existing literature indicates potential shared multifactorial etiologies between dental/periodontal health and CAD. This work aimed to inspect the link between oral hygiene (dental health and periodontal health) and CAD confirmed by coronary angiography. **Materials and methods:** This single-center study recruited 118 patients from the Shahid al-Mihrab Center for Interventional Cardiology. All participants were diagnosed with CAD and scheduled for coronary angiography by cardiologists. Blood tests were performed upon admission to assess creatinine, urea, and white blood cell (WBC) counts using standard methods. Dental health was estimated using the specific index of "Decayed, Missing, Filled Teeth (DMFT)". Periodontal health was assessed based on clinical attachment loss (CAL), defined as the space between the cement-enamel zone and the junctional epithelial attachment. The analysis of variance (ANOVA) employed to inspect continuous variables, while the chi-square test was used to inspect the categorical variables. Descriptive data included the mean and standard deviation to present continuous variables and frequency and percentage present categorical parameters. A p-value less than 0.05 was measured as significant. **Results:** The study population with CAD exhibited poor periodontal health, with 90.7% presenting with localized or generalized periodontitis, half of which were moderate-to-severe cases. Similarly, poor dental health was evident, reflected by a high overall DMFT index (14.6 ± 4.7). Approximately two-thirds of the patients had a DMFT score exceeding 9, indicating a loss of two-thirds of their total dentition. A statistically significant direct association (p=0.004) was observed between dental status and number of critical coronary arterial stenosis. Additionally, a strong direct association (p=0.003) was exposed between the severity of periodontitis and the number of critical coronary arteries stenosis. The association between stages of periodontitis and the number of critically stenosed coronary arteries was positive but not significant (p > 0.05). **Conclusions:** This study reveals an association between oral health (dental and periodontal health) and obstructive CAD in patients undergoing coronary angiography. A significant strong correlation was identified between dental status and periodontitis severity with the occluded coronary arteries. The association between stages of periodontitis and the number of critical stenosis was positive but not statistically significant.

Keywords: oral hygiene, dental health, periodontal diseases, DMFT, CAD, angiography.

INTRODUCTION:

Several studies have inspected the potential link between poor oral hygiene and an increased risk of CVD[1,3]. A 2024 review article in the American Journal of Medicine aimed to update the current understanding of this association.[4] Another study published in 2018, which analyzed data from nearly one million people, revealed a moderate association between CAD and dental loss (a measure of poor oral state). Nevertheless, this connection largely disappeared when accounting for smoking status.[5] A 2022 review in Frontiers in Physiology recognized a rise in the count of lost teeth in subjects with CAD compared to those without the disease. The review also discussed efforts in current years to determine the pathogenesis of causality between oral pathogens and atherosclerotic disease, though an underlying link has not yet been recognized.[6] A 2021 study found that missed teeth are independently associated with poor outcomes in stable CAD.[7] Another study printed in 2022 provided a systematic review analysis of the association between atherosclerosis and oral infections, emphasizing the contemporary gaps and challenges to guide future research.[6] Despite the strength of existing risk prediction models, a significant

population of CVD cases occurs in people without classic potential risk factors. The prevalence of poor oral hygiene, including tooth decay and periodontal disorders, is linked with increased CVD risk. [8] Nevertheless, this does not necessarily imply a causal link, as poor oral health state may be more prone to be a 'risk marker' for cardiovascular diseases, indicating underlying arteriosclerosis rather than an independent cause. A 2004 study published in the Medical Journal of Babylon found that Iraqi subjects with CAD aged 35-70 years had severe periodontal disease compared to healthy controls. [9]

In summary, while the link between CAD and poor oral health state has been well-documented, the nature of this relationship remains unclear, and there is a lack of data specifically examining this relationship in the Iraqi population. Further research is needed to clarify whether poor oral health is a causal factor, a risk factor, or simply a coincidence in the development of CVD. Therefore, this study was intended to inspect the link between oral health and obstructive CAD confirmed by coronary angiography in an Iraqi population. The cross-sectional design allows for an assessment of the strength of this relationship, though causality cannot be inferred.

MATERIALS AND METHODS:

The study is a single center, patients (n=118) were recruited from the Shahid al-Mihrab Center for Interventional Cardiology from February to July 2020. Patients were diagnosed with CAD and had prearranged hospitalization by cardiologists for further cardiac catheterization. Body mass index (BMI) measurement, smoking habits, arterial hypertension, and diabetes mellitus had been registered.

All blood analyses were performed on the day of admission and assessed for creatinine, urea, and WBCs using a traditional technique. Cardiac catheterization was completed using a standard technique. [10] Based on the "2014 American College of Cardiology and American Heart Association published guidelines" to evaluate grades of coronary occlusion. Obstructive CAD is considered when the luminal stenosis is more than 50% for the left main coronary or more than 70% for the other coronaries. The degree of coronary stenosis was divided according to the number of occluded coronary vessels (1, 2, or 3). At best, 2 expert angiographers examined vascular imaging. The index of dental health was the sum of decayed, filled, and missing teeth (DFMT-index)

(11). The periodontal guide was a presence of "clinical-attachment-loss (12)" defined as the dental space from the junctional epithelial attachment' to the cementoenamel junction. [7, 13]

The severity of periodontitis was classified into 3-classes: healthy gum, localized, and generalized gum inflammation. Likewise, the stages of periodontitis were subdivided based on CAL into 4-stages: stage 0 or normal (less than 2mm), stage 1 or mild (2-3mm), stage 2 or moderate (4-5mm), and stage 3 or severe when CAL was more than 5mm.

All statistical breakdowns were verified with SPSS software, version 27. ANOVA tests were studied for continuous variables and the chi-square for dichotomous variables. Mean/SD was presented to define continuous parameters, and frequency/percentage was applied to define categorical parameters. A p-value of $< 5\%$ designates statistical significance.

Informed permission at the start had been obtained from each participant (or family associate). The entire work was approved by the health directorate of Babil. The study protocol is also permitted by the local review board of the Heart Center.

RESULTS:

The study displayed that those with CAD exhibited poor periodontal state. Around 90.7% of patients had localized or generalized periodontitis, while half of them had moderate-severe forms of periodontal inflammation. Equally, poor dental health was reflected by a high overall DMFT index (14.6±4.7). Around $2/3^{rd}$ of the patients had a DMFT score >9 and lost 2/3rd of their total teeth. The study patients were aged 62.9 years, ranging from 27 to 79 years (77.1% male). The ischemic cardiac segments were as follows: 41% were inferior, 38% anterior, 10% inferolateral, and 11% the uncategorized site (results not shown). The incidence of smoking was relatively high among the patients with (40.4%) being current smokers. More than half of the patients were hypertensive, and 42.1% were diabetic. The gender revealed no impact on periodontal and dental health among studied participants (results not shown). Most of the CAD patients were overweight, reflected by their high BMI (28.1 kg/m2). Biochemical assays of urea nitrogen and creatinine were within accepted values, with a high WBCs count, (Table 1).

Table 1: Demographic and clinical baseline appearances of the studied participants		
	Mean	Std. Deviation
Age (years)	62.9	13.4
Male Sex no %	91 (77.1)	
Current Smokers no %	48 (40.4)	
BMI (Kg/m2)	28.1	5.2
WBCs	10.3	3.9

Urea Nitrogen mg/dl		14.9		26.3
Creatinine mg/dl		0.78		0.63
DM no %		50 (42.1)		
HT no %		57 (58)		
Number of affected vessels by coronary angiography				
One vessel no %		30 (25.4)		
One-Two vessel no %		31 (26.3)		
Three vessels or more no %		57 (48.3)		
Periodontal health status				
Severity no %	Normal	11 (9.3)		
	Localized/generalized	107 (90.7)		
Staging no %	Normal/mild	55 (46.6)		
	Moderate/severe	63 (43.4)		
Dental health status				
Total DMFT scoring		14.6		10.7
DMFT Classes no %	1-4	26 (22)		
	5-9	15 (12.7)		
	> 9	77 (65.3)		
DMFT Components	Decayed teeth	2.8		3.3
	Missed teeth	11.7		9.2
	Filled teeth	0.8		1.1
	Total teeth	20.2		10.4

The study revealed a highly significant association (0.004) between dental oral status and the number of critical coronary arteries stenosis (Table 2).

Table 2: Classes of DMFT scoring distributed according to the number of stenosed coronary arteries

Number of affected coronary vessels	Classes of DMFT scoring			Total	P-value
	1-4	5-9	More than 9		
1-vessels	4 (26.7)	2 (13.3)	9 (60)	15	
1-2 Vessels	1 (7.1)	3 (21.4)	10 (71.4)	14	0.004
3 or more Vessels	1 (3.8)	1 (3.8)	24 (92.3)	26	
Total	6	6	43		

The number of significantly stenosed coronary arteries and the degree of periodontitis were shown to be positively correlated (0.003) in the study (Table 3).

Table 3: Severity of Periodontitis distributed according to the number of coronary artery stenosis

Number of affected arteries	Severity of Periodontitis			Total	P-value
	Normal	Localized	Generalized		
1-vessels	0	2 (7.7)	28 (92.3)	30	
1-2 Vessels	0	15 (50.0)	16 (50.0)	31	0.003
3 or more Vessels	2 (3.8)	2 (3.8)	53 (92.3)	57	
Total	2	19	97	118	

There was a non-significant positive association (>0.05) between stages of periodontitis and the number of critically stenosed coronary arteries (Table 4).

Table 4: Stages of Periodontitis distributed according to the number of affected coronary vessels

Number of affected vessels	Staging of Periodontitis				Total	P-value
	0	1	2	3		
1-vessels	2 (7.1)	13 (42.9)	4 (14.3)	11 (35.7)	30	
1-2 Vessels	0	18 (57.1)	9 (28.6)	4 (14.3)	31	> 0.05

3 or more Vessels	2 (3.8)	20 (34.6)	20 (34.6)	15 (26.9)	57	
Total	4	51	33	30	118	

DISCUSSION:

The main goal of this study was to inspect the association between oral health, including periodontal and dental parameters, and the presence of CAD confirmed by coronary angiography in an Iraqi patient population. The oral hygiene and periodontal health of the study participants were generally poor. The data analysis revealed significant associations between various dental health indicators and the presence of obstructive CAD. Specifically, the severity of periodontal disease, but not necessarily the disease stage or grade, was found to be a risk indicator for the presence of obstructive coronary lesions. These findings provide compelling evidence supporting a link between suboptimal oral health and an increased likelihood of obstructive CAD in this population. However, the cross-sectional study design precludes the ability to infer causality. Additional longitudinal research is warranted to elucidate the potential mechanisms underlying this relationship and determine if improvements in oral health could translate to reduced cardiovascular disease risk. Although the basic pathogenesis explaining the relation of poor dental state with CAD remains unclear, supporting earlier findings have shown that gum diseases progress gradually and are characterized by enduring inflammation that leads to bony damage and, ultimately, dental loss. [11] Worthy of mention are CAD and teeth infections sharing common risk factors, for instance, low socioeconomic status, smoking, and diabetes mellitus. [11, 14, 15] A closer look at the study outcomes exposed unfavorable periodontal parameters in patients with poor dental hygiene. As well, the CAD patients had fewer reserved total teeth. The periodontal status in both phenomena could have improved if the teeth had been extracted because of the impacts of progressive periodontitis. (12). Though still debatable, several observational and clinical studies have found links between dental health and CAD. [11, 14, 16] The trial from South Korea directed by Ho Lee et al. revealed that patients with obstructive CAD have significantly more dental loss than healthy subjects, even if obstructive coronary disease was not related to all other dental indices, including the DFT. [16] Zanella et al. from Brazil found that dental loss was significantly related to an increased chance of developing an obstructed CAD. [17] The same study failed to show significant associations between periodontitis and obstructed CAD. However - unlike our outcomes-, there was no difference in CAD patients with <10 teeth compared to those with >10 teeth reported in an Austrian study published in 2011, even when adjusting for other confounders.[18] A longitudinal trial by DeStefano et al. involved 9760 American adults

and exposed that dental disease is linked with a greater risk of CAD, mainly in young males. [19]

Chronic dental inflammation was considered the primary pathophysiology of arteriosclerosis and subsequent CAD. [20] It has to be pointed out that details of extracted teeth have been registered in the dental form. Yet, just a few patients with missed teeth were attentive to them. The details for dental extractions were checked check in the dental inquiry form. However, only a limited number of patients with missed teeth were aware of them. In numerous previous studies, missing teeth had been considered an indicator of the presence of a past periodontal disease or the terminal stage of it, a belief that our results also recommend.

The association between gum disease and coronary diseases has been considered broadly. The CAL is regarded as the gold standard to express periodontal damage and has been suggested as the signifier for periodontic disease .[21] A consensus statement in 2013, from a shared workshop included the "European Federation of Periodontology" and the "American Academy of Periodontology" that there is a constant indication from clinical trials supporting the opinion that periodontitis raises the risk for coronary vascular events. [22] However, limited studies have evaluated the link between periodontitis and CAD identified by angiography. A recent study from Poland reported that the oral hygiene of CAD patients (proved by coronary angiography) was significantly worse than that of healthy subjects. [23] Along a similar line, another study from Poland also exposed that poor periodontal health waves were observed in patients with CAD compared to healthy people, and greater severity of periodontitis was linked with a risk factor for CAD.[24] Likewise, a relationship between periodontitis and CAD has been recognized in a study conducted in Northern Ireland on middle-aged men and was independent of DM and other confounder potential factors. [12]

As a rebuttal to this point, two other studies had failed to identify any relations between the several periodontal variables with CAD. [17, 25] This inconsistency can be clarified by variations among study policies, including criteria for defining periodontal disease and sample features. Henceforth, and to avoid any bias in evaluating periodontitis; the use of a full intra-oral protocol is crucial. [26] Other researchers have reported unfavorable effects of periodontitis with CAD through the "Community Periodontal Index" of Treatment Needs and "Probing depth in Ramfjord teeth", or by assessing 4-6 dental sites. [17] Moreover, the conflicting outcomes might be due to variations in the cardiovascular profiles of the patients studied. Likewise, there was likely some

missorting caused by imprecisions of oral examination; still, this was dubious as the main factor in identifying those with poor periodontal status. Another source of imprecision in oral health; is bleeding gum, which may be due to several patients being on antiplatelet medications .[12]

Supporting our outcomes; is evidence that proposes that cigarette smoke is the major risk factor for periodontal diseases, and it has been appraised that >50% of long-lasting periodontitis can be ascribed to tobacco smoke. (27). Furthermore, cigarette smoke is one of the potential factors for CAD. Hence, it was expected to have been a vital confounder in any assumed association between CAD and periodontitis. Yet, a previous study has revealed a strong link between CAD and periodontitis even in non-smokers. [28]

The approvals for anticoagulant use by "Federal Drug Administration" recommend a long-term prescription for preventing thrombotic events in high-risk subjects. [29] An initial critical decision in the management of CAD – is whether to interrupt anticoagulants or not – during an angiography study. [30] Such interrupted oral anticoagulant use can affect oral health, particularly gum health and periodontal status, which can misinterpret the state of oral hygiene in the current study. There was no influence of gender on the variables. This is partly due to the cross-sectional strategy of the current research did not permit any causal extrapolations. Additionally, the high incidence of smoking in this study (40.4%) may be associated with poor oral hygiene. To the best of the authors' data, this work is the first to appraise the relationship between oral health (defined by periodontal and dental status) and CAD assessed by angiography .

Importantly, the results of this study indicate that patients who undergo coronary angiography tend to express poor oral hygiene, independent of the associations examined. These findings highlight the necessity for improved oral care among cases of CAD. As well as greater awareness and collaboration between cardiologists and dentists to prioritize the oral health of this high-risk patient group.

CONCLUSION:

Improving oral hygiene and periodontal health may represent a modifiable risk factor for cardiovascular disease that could be targeted through enhanced patient education and collaboration between dentists and cardiologists. If a causal link is established, the study findings would have important public health implications. However, further research is desirable to confirm these associations and explain the potential mechanisms before definitive clinical recommendations can be made.

REFERENCES:

1. Al-Hindy Hayder AM A-MA, Mousa MJ. Association of dental caries in the era of COVID-19 with the number of occluded coronary vessels: A non-traditional risk factor in patients with acute coronary syndrome. Journal of Emergency Medicine, Trauma & Acute Care. 2023;3:1-7. doi: 10.5339/jemtac.2023.midc.8.

2. Al-Saad R, Shaker, AK, Dleikh, FS, Al-Hindy, Hayder AA Is there any association between highly sensitive C-reactive protein and dental-status in ischemic heart diseases Comparative-study Biochem Cell Arch. 2020;20:6069-75.

3. Hayder Abdul-Amir Maki Al-Hindi SFA-S, Basim MH Zwain, Thekra Abid Al-Kashwan Jaber. Relationship of Salivary & Plasma Troponin Levels of Patients with AMI in Merjan Medical City of Babylon Province: Cross-Sectional Clinical Study. Magazine of Al-Kufa University for Biology. 2016;8:53-8.

4. Hopkins S, Gajagowni S, Qadeer Y, Wang Z, Virani SS, Meurman JH, Krittanawong C. Oral Health and Cardiovascular Disease. The American Journal of Medicine. 2024;137:304-7. doi: 10.1016/j.amjmed.2023.11.022.

5. Batty GD, Jung KJ, Mok Y, Lee SJ, Back JH, Lee S, Jee SH. Oral health and later coronary heart disease: A cohort study of one million people. Eur J Prev Cardiol. 2018;25:598-605. doi: 10.1177/2047487318759112. PubMed PMID: 29461088; PubMed Central PMCID: PMCPMC5946673.

6. Bezamat M. An updated review on the link between oral infections and atherosclerotic cardiovascular disease with a focus on phenomics. Front Physiol. 2022;13:1101398. doi: 10.3389/fphys.2022.1101398. PubMed PMID: 36589419; PubMed Central PMCID: PMCPMC9794572.

7. Al-Mumin A, Al-Hindy, Hayder Abdul-Amir Maki. Hyperuricemia has a deleterious role in patients with acute coronary syndrome presented with poor oral hygiene. International Journal of Pharmaceutical Research. 2020;12:1196-202.

8. Hayder Abdul-Amir Makki Al-Hind GMR, Mohammed Ihsan Chabuk, Amal Talib Al Sa' ady, Safa Jihad, Suhad Hafidh. Brush Up Your Teeth to Brush Up Your Heart: A Clinical Review on the Association of Oral Hygiene with Cardiovascular Diseases. International Journal of Innovative Science and Research Technology. 2021;6:669-76. doi: bit.ly/330O3nV.

9. Al-Rawi N, Mal-Weheb A. Association between periodontal health status and acquired coronary heart disease. Mustansiria Dental Journal. 2004;1:202-9. doi: 10.32828/mdj.v1i2.1118.

10. Janket SJ BA, Chuang SK, Jones JA.. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95:559–69.

11. Raghdan Z. AKS, Dleikh F., Al-Hindy H. Is There Any Association Between Highly Sensitive C-Reactive Protein and Dental-Status in Ischemic Heart Diseases? A Comparative Study. Biochemical and Cellular Archives. 2020;20:6069-75.

12. Briggs JE. PP, Vivienne L.S., Jayne V., Robert W., Alun E., and Gerard J. Angiographically Confirmed Coronary Heart Disease and Periodontal Disease in Middle-Aged Males. J Periodontol. 2006;77:95-102.

13. Lee H, Kim HL, Jin KN, Oh S, Han YS, Jung DU, et al.Kim MA. Association between dental health and obstructive coronary artery disease: an observational study. BMC Cardiovasc Disord. 2019;19:98. Doi: 10.1186/s12872-019-1080-9. PubMed PMID: 31029089; PubMed Central PMCID: PMCPMC6487007.

14. Hayder Al-hindi SFA-S, Basim MH Zwain, TAA-KJ. Relationship of Salivary & Plasma Troponin Levels of Patients with AMI in Merjan Medical City of Babylon Province: Cross-Sectional Clinical Study Al-Kufa Univ J Biol. 2016;8:6.

15. Samer MM. AS, Hayder AA., Mazin JM. C-Reactive Protein is Associated with the Severity of Periodontal Disease — An Observational Study Among Acute Myocardial Infarction Patients. Sys Rev Pharm 2020;11:252-7.

16. Ho Lee H-LK, Kwang Nam Jin. et al. Association between dental health and obstructive coronary artery disease: an observational study. BMC Cardiovascular Disorders. 2019;19:7.

17. Zanella SM PS, Barbisan JN, Vieira L, Saba-Chujfi E, Haas AN, R€osing CK. . Periodontal disease, tooth loss and coronary heart disease assessed by coronary angiography: a cross-sectional observational study. J Periodont ResJ. 2016;51:221–7.

18. Robert B. JA, Peter S., Gerald K., Stephen F., John S., Helmut S., Serge P. Periodontal and coronary heart disease in patients undergoing coronary angiography. Metabolism Clinical and Experimental. 2011;60:127–33.

19. DeStefano F, Anda RF, Kahn HS, Williamson DF, Russell CM. Dental disease and risk of coronary heart disease and mortality. Bmj. 1993;306:688-91. doi: 10.1136/bmj.306.6879.688. PubMed PMID: 8471920; PubMed Central PMCID: PMCPMC1677081.

20. Yesar MH. Al-Shamma AA, Hayder Abdul-Amir Al-Hindy. Caries Burden is associated with serum uric acid and CRP in Patients Treated for Acute Coronary Syndrome. Journal of Chemical Health Risks. 2022;12.

21. Tonetti MS, Claffey N. Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research. Group C consensus report of the 5th European Workshop in Periodontology. J Clin Periodontol. 2005;32 Suppl 6:210-3. doi: 10.1111/j.1600-051X.2005.00822.x. PubMed PMID: 16128839.

22. Tonetti MS TVD. A working group of the joint EFPAAPw. Periodontitis and atherosclerotic cardiovascular disease: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases. J Clin Periodontol. 2013;40:S24–S9.

23. Katarzyna S. JP, Skoglund S., Suvi V., Piotr J. The oral health of patients with acute coronary syndrome is confirmed using coronary angiography. Pol Med J. 2020;XLVIII:23–6.

24. Agnieszka W. TZ, Joanna WM. and Andrzej P. The inflammation link between periodontal disease and coronary atherosclerosis in patients with acute coronary syndromes: a case-control study. BMC Oral Health. 2020;21:17.

25. Malthaner SC, Moore S, Mills M, Saad R, Sabatini R, Takacs V, et al.Oates TW, Jr. Investigation of the association between angiographically defined coronary artery disease and periodontal disease. J Periodontol. 2002;73:1169-76. doi: 10.1902/jop.2002.73.10.1169. PubMed PMID: 12416775.

26. Kingman A, Susin C, Albandar JM. Effect of partial recording protocols on severity estimates of periodontal disease. J Clin Periodontol. 2008;35:659-67. doi: 10.1111/j.1600-051X.2008.01243.x. PubMed PMID: 18513337.

27. Tomar SL, Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. National Health and Nutrition Examination Survey. J Periodontol. 2000;71:743-51. doi: 10.1902/jop.2000.71.5.743. PubMed PMID: 10872955.

28. Rutger Persson G, Ohlsson O, Pettersson T, Renvert S. Chronic periodontitis, a significant relationship with acute myocardial infarction. Eur Heart J. 2003;24:2108-15. doi: 10.1016/j.ehj.2003.10.007. PubMed PMID: 14643271.

29. Qayssar Joudah Fadheel RTN, Hayder Abdul-Amir Al-Hindy. Evaluation of Practice of Prescribing and Monitoring Anticoagulants Among Hospitalized Iraqi Patients. HIV Nursing. 2022;22:71-6.

30. Venetsanos D, Skibniewski M, Janzon M, Lawesson SS, Charitakis E, Böhm F, et al.Alfredsson J. Uninterrupted Oral Anticoagulant Therapy in Patients Undergoing Unplanned Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2021;14:754-63. doi: 10.1016/j.jcin.2021.01.022. PubMed PMID: 33826495.