Observational Study Among Coronary Artery Diseases Patients: Provable Correlation of Ultra-Sensitive CRP with Oral Health Behavior

Mahir A .Alzughaibi,* Ammar w. Obeid,* Nassar A. Mera*

*** MOH-Merjan teaching hospital**

Abstract

Background: C-reactive protein (CRP) has been known as a marker of inflammation and applied as a risk biomarker of patients with coronary artery diseases (CAD). Of interest, was the association of CRP to OHB and CAD mutually. This study aimed to evaluate the correlation of oral health behavior (OHB) of patients with CAD and compare this with that of a provably healthy control group.

Methods: 136 patients who were managed as CAD took part in the study. A healthy control group, made up of 74, had recruited following matching for age and gender with the patients' group. The dental examination of all enrolled participants comprised the dental status (DMFT scoring) and periodontal disease (PD) status using Clinical attachment loss. Likewise, in all subjects, the levels of serum ultra-sensitive CRP (US-CRP) had evaluated. Statistical evaluation: t-test, chi-squared test, regression analysis, ANOVA analyses (level of significance $p<0.05$) had completed using SPSS-25.

Results: The mean DMFT of the CAD-group (13.7±9.8) and the Control group (5.1±4.8) showed a significant difference (p-0.05). A significantly higher average loss of teeth in the CAD-group (10.9±8.9 vis 3.3±3.3). Both the grades and stages of PD were statistically worse among CAD-group (p-0.001). The levels of serum US-CRP were significantly higher in patients with CAD compared to the controls.

Conclusion: The levels of serum US-CRP were significantly higher in patients with CAD. The state of OHB in patients with CAD significantly differed from that of the control. Patients with CAD displayed more signs of PD and a higher dental loss.

Keywords: Coronary artery diseases, DMFT, Periodontal disease.

Introduction

Oral health behavior (OHB) includes two entities: periodontal diseases (PD) -the most common diseases of the mouth- together with the dental state (DS); both conditions represent the chief cause of dental loss [1-4]. PD is a widespread, multifaceted, insidious inflammatory condition of the paradental supportive tissue, began as bacterial biofilm then arose mostly by distressed host immunity and progressing gingiva loss [5, 6]. Henceforth, inflammation is a characteristic finding of PD, in which microbes and their byproducts are the leading etiologic agents [7]. Some arguments can be advanced to support that OHB, especially the presence of PD, increases the risk of occurrence of coronary artery disease (CAD) [2].

Dental caries is a lifetime, multifactorial disorder, and denoted as one of the primary worries of the world about OHB [8]. The data yielded by numerous scholars provides convincing evidence of the causal-effect relationships between inflammation and DS [9]. Similarly, a rapidly growing literature indicates the associations of DS with CAD [2, 10]. CAD is the principal cause of illness and

death in the industrial states universally [11, 12]. It is a pathology of complex basis accompanied by a well-known inflammatory role in the arterial wall [13, 14].

A linkage between OHB and CAD has been assumed for more than a century [15]. Of late, a concern of probable links between PD and CAD has strengthened (perhaps by increasing the inflammatory burden of people) and was driving an energetic field of study into probable relation and causality [2].

Pro-inflammatory factors, such as C-reactive (CRP) have been raised in patients with PD [15] or with poor DS [8, 16] and in patients with CAD [12, 14, 17]. CRP is a broad-based quantitative systemic inflammation readout [18, 19]. The precise influential role of CRP in CAD is uncertain. Still, its immunoreactivity had linked to susceptibility and dislodgment of thrombotic plaques [5]. In the light of the aforesaid piece of evidence, the number of signs approving an association between OHB and CAD continues to grow. Hence, this investigation aimed to evaluate the correlation of the CRP with OHB (in terms of PD and DS) of patients with CAD in a case-control observational study.

Subjects and methods:

Participants and study design

Study subjects of this case-control study comprised the attendants of Shahidul-Mihrab interventional cardiac center. The study enrolled 136 patients identified as CAD with sex and age-matched 74 seemingly healthy people selected from the patients' associates. All participants completed oral inspection. The time between the arrival until the blood sampling to evaluate CRP was < 24 hours.

Assessment of oral health behavior (OHB)

A proficient examiner finalized oral inspection using a particular dental-mirror and explorer. Grading of PD had implemented based on "a new classification outline for periodontial and preimplant diseases: Introduction and key changes from the 1999-classification" [20]. While, the severity of PD had implemented by using a discrete probe to evaluate "clinical-attachment-loss (CAL)" of the gingival separation from the alveolar edges in millimeters (mm) [21, 22].

The dental checkup had performed by using a WHO-verified dental (DMFT) score [23]. The occluded dental facades were washed with a soft brush and examined after drying by mirror and explorer to yield precise DMFT-scores.

Grouping of study candidates

The studied candidates had divided into trio-grades of PD: normal-gum, localized PD, and generalized PD. Likewise, the severity of PD had subdivided according to CAL into four stages: healthy or normal-gum (< 2mm), mild PD (2-3mm), moderate PD (4-5mm), and severe PD when CAL was > 5mm. Likewise, candidates classified into 3-classes based on DS: a DMFT measure of (1-4) indicates low, (5-9) is moderate, and > 9 is severe caries status [10, 24].

Ethical approval

As soon as the patient becomes stable, a written consent form had signed within the first 24 hours after the admission. The whole investigation had permitted by the local ethical committee for research at the health directorate. The entire study is corresponding to the scruples of the Helsinki-Declaration.

Assessment of ultra-sensitive C-reactive protein (US-CRP)

The levels of US-CRP had scrutinized using an ultra-sensitive immunoturbidimetry-assay and an

immunology analyzer (Roche Diagnostics®), Cobas c111- USA. This technique provides measurements ranging from 0.1 up to 500 mg/L. The hematological investigation had carried out at the hospital's main biochemical laboratories.

Statistical Investigation

The statistical studies had achieved using SPSS/23-USA, with a significance-value premeditated at 0.05. The quantitative parameters were demonstrated as mean±SD, although categorical parameters as (frequency and percentage). Compared percent of the presence of risk factors across the groups had confirmed with *the chi-square* test. Associations between US-CRP level and PD (stages and grades) had been scrutinized by linear-regression.

Results

Baseline demographics of the population

The baseline demographic variables of the studied applicants had exposed in table-1. The overall mean ages were 52.3±16.1 years, 167 (79%) were males. At baseline, 72 (31.2%) were current smokers, 67 (31.9%) were diabetics, and 73 (34.8%) were hypertensives. The control group was younger (p-0.05), lower systolic and diastolic blood pressure (p-0.05), had the same BMI and sex distribution, but was higher than CAD patients on percent being a current smoker (p-0.05) as well as lower incidence of diabetes and hypertension significantly (p-0.05). As well, the CAD group had significantly higher mean levels of US-CRP than the control (p-0.001) in particular high-risk levels.

Table-1: Matching characteristic of the participants of both coronary artery diseases and healthy control groups

Variables	Total (210)	CAD patients (N=136)	Control subjects (N=74)	Significance
Age/years	52.3±16.1	59.3±13.8	39.5±11.3	0.05
Male sex (No %)	167 (79)	104 (76.5)	63 (85.1)	NS
BMI (Kg/m^2)	28.3±5.0	27.2±5.0	26.7±0.4	NS
Smoking (No %)	72 (31.2)	54 (39.7)	18 (24)	0.05
Systolic BP (mmHg)	142±11.5	149±8.9	131±0.5	0.05
Diastolic BP (mmHg)	92±1.9	104±4.1	82±0.9	0.05
Ultra-Sensitive-CRP	4.7±6.1	8.2±6.7	1.1±0.7	0.05
Low risk < 1 mg/L (No %)	49 (30.9)	7 (5.3)	42 (56.8)	0.001
Average risk 1-3 mg/L (No %)	39 (23.5)	9 (6.7)	30 (40.5)	0.001
High risk > 3 mg/L (No %)	122 (45.6)	120 (88)	2 (2.7)	0.001
Diabetes mellitus (No %)	67 (31.9)	59 (43.4)	8 (10.8)	0.05
Hypertension (No %)	73 (34.8)	68 (50)	5 (6.8)	0.05

There was no impact of gender on the distribution of study parameters among the two groups. Nevertheless, significantly higher mean levels of US-CRP with a higher incidence of hypertension and smoking among all male subjects (p>0.05) were observed (results not shown).

Assessment of oral health behavior (OHB)

Periodontal status: the poor periodontal state was evident among patients with CAD. That had mirrored significantly by worse grades and the stages of PD [aside from mild PD, which was more frequent among the controls].

Dental status: an unfavorable DS was also apparent among patients with CAD, although the overall DMFT-index in all participants was 10.7±9.4. The inferior DS among patients mirrored by significantly elevated DMFT-scores compared to controls [13.7±9.8, vis

5.1±4.8, p-0.05 one-to-one]. On top, all DMFT components were imperfect among CAD (P<0.05 for each comparison), except for the incidence of decayed teeth (table-2).

Table-2: Oral health status differences between patients with acute coronary syndrome and control group

Parameters of Oral Health Status	Total (210)	CAD patients (N=136)	Healthy control (N=74)	*P-value*
Grades of Periodontal diseases				
Normal (No %)	62 (29.5)	47 (75.8)	15 (24.2)	0.003
Mild (No %)	81 (38.6)	24 (29.6)	57 (70.4)	0.05
Moderate (No %)	38 (18)	35 (92.1)	3 (7.9)	0.001
Sever (No %)	29 (13.9)	29 (100)	0	0.001
Stages of Periodontal Diseases				
Normal (No %)	62 (29.5)	14 (79.7)	48 (20.3)	0.05
Localized (No %)	27 (12.9)	19 (29.2)	8 (70.8)	0.004
Generalized (No %)	121 (57.6)	101 (82.9)	20 (17.1)	0.001
Dental Health Status				
DMFT (mean±SD)	10.7±9.4	13.7±9.8	5.1±4.8	0.05
Missing (mean±SD)	8.3±8.3	10.9±8.9	3.3±3.3	0.05
Decayed (mean±SD)	2.1±2.6	2.4±2.5	1.7±2.9	NS
Filled (mean±SD)	0.6±1.4	0.7±1.7	0.3±0.7	0.05

Correlation of US-CRP with diabetes and hypertension

The data gathered suggests a significant relationship between US-CRP and diabetes (*p*-0.024) among CAD patients. In the meantime, a positive nonsignificant association (p-0.28) between US-CRP and hypertension had observed among patients (table-3).

Table-3: Correlation of ultra-sensitive CRP to diabetes mellitus and hypertension in ACS and healthy control

Grades of US-CRP according to risk levels	Coronary artery diseases				Healthy control			
	Diabetes Mellitus	Present No (%)	Absent No (%)	*P-value*	Hypertension	Present No (%)	Absent No (%)	*P-value*
Low risk < 1mg/L		3 (10.0)	1 (2.2)			3 (37.5)	39 (59.1)	
Moderate risk 1-3 mg/L		4 (13.3)	1 (2.2)	0.024		5 (62.5)	25 (37.9)	0.28
High risk > 3 mg/L		23 (76.7)	43 (95.6)			0	2 (3.0)	

Correlation between US-CRP and oral health behavior (OHB)

Dental status (in terms of means of DMFT and missing teeth) exhibited a positive significant linear association (P-0.000) with the mean US-CRP levels among patients (figure-1).

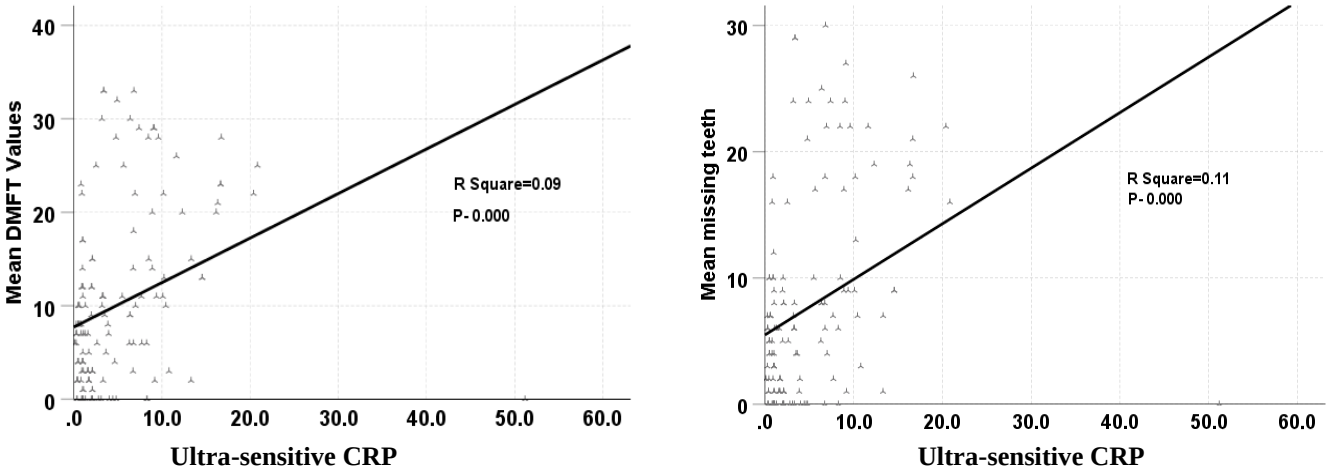

Figure-1: Correlation of mean DMFT values and mean missing teeth with US-CRP levels among

The periodontal status in terms of the grades of PD exhibited a positive weak-association with mean US-CRP levels. Whereas, the stages of the PD showed a positive, significant association with mean US-CRP among all study subjects (figure-2).

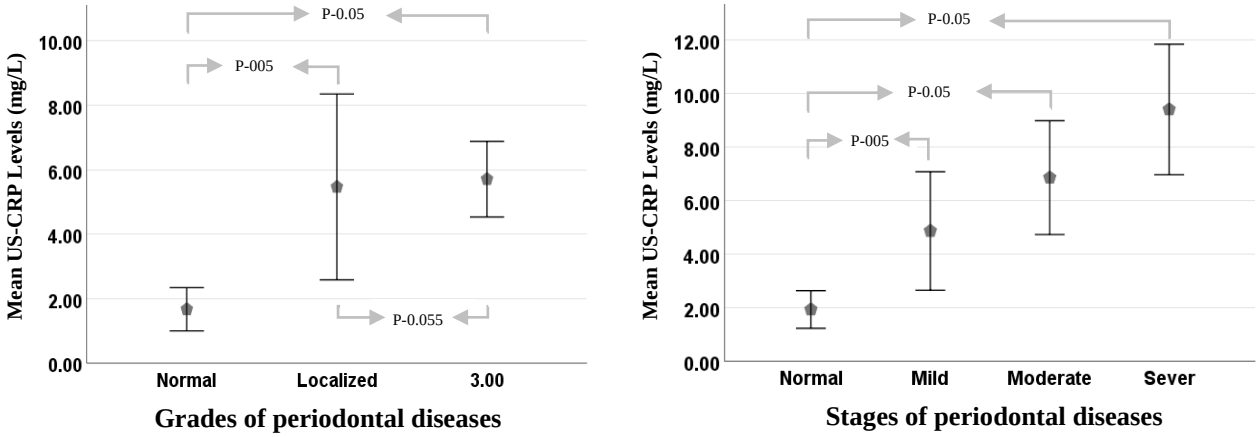

Figure-2: Correlation of mean US-levels to the grades and stages of periodontal diseases among study participants

Discussion:

There is ample support for the claim CRP is a nonspecific inflammatory marker, that is strongly related to the risk of CAD [14, 18]. Several studies highlight a relationship between PD and CRP, concluding that patients with higher PD severity had higher plasma CRP levels [8, 25]. The objective of this case-control research of consecutive 136 survivors of CAD was to assess probable relations between OHB and CAD. It might be clear that the etiologies of poor OH and CAD, age, cigarette-smoking, hypertension, and diabetes [7, 8, 10, 25]. All of the aforementioned-issues may affect OHB and CAD mutually, which may act as confusing factors and even may affect the statistical analysis.

Principally, PD increases the systemic levels of CRP, which may enhance the inflammatory activity in atherothrombotic lesions and consequence potentially increase the risk of CAD [8, 25, 26]. This outcome supports the presence of a direct, pathogenic mechanism between the two pathologies in which PD might influence

CAD by inducing recurrent bacteremia events and activating a local inflammation [27]. Likewise, in a pooled analysis of observational researches, PD seems to be correlated with a higher risk of CAD [28]. Even though the European agreement that the systemic impact of the infective burden of the oral organisms may not associate with the systemic effect, as their amount not proportionate to the systemic exposure to them [26].

Correlation of CRP with diabetes and hypertension

The data gathered in the study suggests a significant relationship between US-CRP and diabetes. With a positive nonsignificant association with hypertension among CAD patients. In another study, hypertension showed a significant association with CRP levels among myocardial infarction patients with PD [29]. Diabetes affects OHB and CRP that revealed higher levels in patients with CAD [30]. Moreover, higher SGLT1-expression in the luminal side of salivary gland ductal cells associates with hyposalivation in diabetic and hypertensive rats that sequentially elevates their susceptibility for poor OHB [31].

The Role of CRP in Oral Health Behavior in Coronary Artery Disease

We hypothesize that CAD patients will have poorer OHB than healthy controls. Dental status (in terms of means of DMFT-index and missing teeth) unveiled a significant linear association with the mean US-CRP levels in our patients, which is in line with several other reports [2, 8, 10, 25]. Supporting our outcomes, a body of research had been growing on the possible link of PD with CAD [5, 15, 25]. Contrary to this, no significant association between PD with the onset of the first myocardial infarction, had shown by other work [32]. CRP is a biomarker of both low-grade inflammations associated with PD, apical lesions of endodontic origin, and atherosclerotic events [33].

Though researchers are consistent, the accurate pathophysiology underlying such links remains an area of debate. Still, inflammation may perhaps be one of the most important shared mechanisms between CAD and DS. Cooperatively, hyperlipidemia, the bioactivity of oral vegetation in coronary-sclerosis and activated protease receptors might be added possible explanations [8, 10]. In contrast, several scholars with diverse studies protocols were unable to show a significant alteration in OHB among CAD patients when compared to healthy control [34, 35].

Several scholars propound the view that some growth factors involved in the inflammatory component of atherogenesis might be induced by CRP activity like transforming growth factor-beta (TGF-β) and platelets derived factor (PDGF). TGF-β is a "cytokine of TGF-β superfamily" that had multidisciplinary cell activities [36, 37]. CRP can induce provocation and cross-talk among toll-like receptor-4 and NF-κB/TGF-β1 signaling-pathway (that has a crucial inflammatory role) in a cardiocytes-model [38]. PDGF belongs to the growth factor family, acts as a forceful mitogen for different cell types [39]. The endogenous CRP might increase the expression of PDGF-receptor and PDGF-mediated chemotaxis. Thus can stimulate the migration of smooth muscle cells (which had a well-known role in atherogenesis) [40]. In turn, CRP binds to phosphatidylcholine-generating long-chain acylcarnitines and lysophosphatidylcholines under the existence of calcium and ultimately causes apoptotic cell death that might further intensify inflammation [41].

Whether these correlations of OHB and CAD have any expressive clinical impact

in the initiation and progression of CAD is indefinite, even supposing infection seems to modify, if not trigger, arteriosclerosis. Nonetheless, further researches had better inspect more systematically the consequence of dental treatment on systemic markers of inflammation and the relations of pro-inflammatory genetic abrasions with OHB and CAD.

Conclusions:

The study verified that patients with CAD exhibited a significantly unfavorable OHB compared to the control. The patients with CAD displayed more signs of PD and a higher dental loss. The levels of serum US-CRP were higher significantly in patients with CAD,

Competing interests: The authors declare that they have no competing interests.

References:

1. JA., O.J., Periodontitis From Dysbiotic Microbial Immune Response to Systemic Inflammation. J Clin Med, 2019. **8**(10): p. 1706.
2. Al-Mumin A., A.-H.H., Hyperuricemia has a Deleterious Role in Patients with Acute Coronary Syndrome Presented with Poor Oral Hygiene. International Journal of Pharmaceutical Research, 2020. **Jan-Jun**: p. 7.
3. Hassan, M., Aamid, B., Hameed, Z., & Hashim, H. , ASSOCIATION OF TRANSFORMING GROWTH FACTOR BETA 1 (TGF-B1) GENE POLYMORPHISM WITH CHRONIC PERIODONTITIS. BIOCHEMICAL AND CELLULAR ARCHIVES, 2019. **19**: p. 2427-243.
4. Al-Dabbagh, N.N., Al-Janabi, W.H., Al-Shuhaib, M.B.S., Identification of Candida species using 26S ribosomal RNA gene sequencing in patients with periodontitis. J Bacteriol Virol., 2019. **49**(4): p. 212-220.
5. MR., T.B.I.R., Periodontal Disease, Inflammation and Atherosclerosis Progression in Patients with Acute Coronary Syndromes – the ATHERODENT Study. J Cardiovasc Emergencies, 2018. **4**(1): p. 17-23.
6. Al-Dabbagh, N.N., Hashim, H.O., Al-Shuhaib, M.B.S.. , A highly efficient computational discrimination among Streptococcal species of periodontitis patients using 16S rRNA amplicons. Korean J Microbiol., 2019. **55**(1): p. 1-8.
7. Hussein. A., Z.B., Thekra A., Hayder A. , Al-hamadawi ZA. Relationship of Periodontitis with Acute Myocardial Infarction: Case Control Study. Al-Kufa Univ J Biol., 2017. **www.uokufa.edu.iq/journals/index.php./ajb/index.**(Special is:57-68).
8. Al-Saad R, S., Shareef F., et al., Is There Any Association Between Highly Sensitive Creactive Protein And Dental-Status In Ischemic Heart Diseases? A Comparative Study. Biochem. Cell. Arch. , 2020. **20**(2): p. 6069-6075.
9. Rôças IN, A.F., Rachid CTCC, Lima KC, Assunção IV, Gomes PN et al., Microbiome of Deep Dentinal Caries Lesions in Teeth with Symptomatic Irreversible Pulpitis. PLoS One, 2016. **11**(5): p. e0154653.
10. HAAM, A.S.A.M., Basim MH Zwain, Decayed, Missed, Filled Teeth Scores in Iraqi Patients with Acute Myocardial Infarctio. Al-Kufa University Journal for Biology, 2016. **8**(3): p. 7.
11. Dhulfiqar A., J.R., AA. Hayder, Obaide A. , Cystatin-C in patients with acute coronary syndrome: Correlation with ventricular dysfunction, and affected coronary vessels. Journal of Contemporary Medical Sciences, 2020. **6**(1).
12. Saheb A., A.A., and MJM, Combined Assessments of Multi-panel Biomarkers for Diagnostic Performance in Coronary Artery Disease: Case-Control Analysis. Sys Rev Pharm, 2020. **11**(6): p. 7.
13. H. M., M.J.M., Al-Kashwan T., Sudan A., SAA-R. , Correlation of on Admission Levels of Serum Uric Acid with Acute Myocardial Infarction: Case : Control Study. J Glob Pharma Technol., 2011. **11**(7): p. 289-294.
14. Maki Alhindi, M.J., Thekra Abid Jaber Al-kashwan, Ahmed Sudan, Saja Ahmed Abdul-Razzaq, On Admission Levels of High Sensitive C-Reactive Protein as A Biomarker in Acute Myocardial Infarction: A Case-Control Study. Indian Journal of Public Health Research & Development, 2019. **10**(4): p. 5.
15. Murtaza Mustafa, Y.R., M.Phanindranath MR, MM.Sien N ooth, Oral Health and its Association with Cardiovascular Disease. IOSR J Pharm., 2015. **5**(2): p. 45-51.
16. J.L. Ebersolea, R.J.K., C. Campbellc, D.F. Kinaned, J. McDevitte, N. Christodoulidesf, P.N. Florianof and

CSM. , Salivary and Serum Adiponectin and CRP Levels in Acute Myocardial Infarction Related to BMI and Oral Health. J Periodontal Res., 2017. **52**(3): p. 419–427.
17. TB., R.A.R., Evaluation of the association between chronic periodontitis & acute coronary syndrome: A case control study. J IndSocPer., 2013. **17**(2): p. 210-213.
18. Hajir K., D.F., Al-Aaraji A., Hayder M., Mousa M., Biochemical causal-effect of circulatory uric acid, and HSCRP and their diagnostic correlation in admitted patients with ischemic heart diseases. Journal of Cardiovascular Disease Research 2020. **11**(4).
19. Jawad Q. , B.H., Hamid N., & HA-A M. , High-Sensitivity C-reactive protein Assessment in Bronchial Asthma: Impact of Exhaled Nitric Oxide and Body Mass Index. Sys Rev Pharm, 2020. **11**(3): p. 705-711.
20. CatonJ, A., Berglundh T et al. . , A new classification scheme for periodontal and peri-implant diseases and conditions – Introduction and key changes from the 1999 classification. J Periodontol., 2018. **89**: p. 1-8.
21. Papapanou, P.N.e.a., Periodontitis: Consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. J Periodontol., 2018. **89**: p. S173-S182.
22. PT., F.A.o., Report on the Update to the 1999 Classification of Periodontal Diseases and Conditions. J Periodontol., 2015. **86**(7): p. 835-838.
23. WHO, World Health Organization,oral health survey: basic methods. Third Edition ed: Geneva; . 1987.
24. Patel RN, E.K., Pitts N, Schulte A, Pieper K WS. , Variation in methods used to determine national mean DMFT scores for 12-year-old children in European countries. Community Dent Health, 2016. **33**: p. 286-291.
25. Samer M., A.S., Hayder A., Mazin J. , C-Reactive Protein is Associated with the Severity of Periodontal Disease — An Observational Study Among Acute Myocardial Infarction Patients. Sys Rev Pharm 2020. **11**(10): p. 252-257.
26. Uriza, C.L., et al., Ultra-Sensitive C-Reactive Protein (US-CRP) in Patients With Periodontal Disease and Risk of Acute Myocardial Infarction. Cardiol Res, 2011. **2**(1): p. 27-35.
27. Haraszthy, V.I., et al., Identification of periodontal pathogens in atheromatous plaques. J Periodontol, 2000. **71**(10): p. 1554-60.
28. Xu, S., et al., The association between periodontal disease and the risk of myocardial infarction: a pooled analysis of observational studies. BMC Cardiovasc Disord, 2017. **17**(1): p. 50.
29. El-Beshbishy, H.A., R.A. Maria, and F.A. Bardi, Biochemical and C-reactive protein alterations in myocardial infarction periodontitis patients. Am J Med Sci, 2014. **348**(3): p. 181-5.
30. Arregoces, F., et al., Relation between ultra-sensitive C-reactive protein, diabetes and periodontal disease in patients with and without myocardial infarction. Arquivos brasileiros de endocrinologia e metabologia, 2014. **58**: p. 362-368.
31. Sabino-Silva, R., et al., Increased SGLT1 expression in salivary gland ductal cells correlates with hyposalivation in diabetic and hypertensive rats. Diabetology & metabolic syndrome, 2013. **5**(1): p. 64-64.
32. Rydén L, B.K., Ekstrand E, de Faire U, Gustafsson A, Holmer J, Kjellström B, Lindahl B, and N.Å. Norhammar A, Näsman P, Rathnayake N, Svenungsson E. Klinge B., Periodontitis increases the risk of a first myocardial infarction: a report from the PAROKRANK study. Circulation, 2016. **133**: p. 576–83.
33. Stoian, I.M.a.D., Oral Health and Cardiovascular Disorders, Understanding the Molecular Crosstalk in Biological Processes, in IntechOpen, M.A. El-Esawi, Editor. 2019.
34. al., Z.e., Oral health status of patients with acute coronary syndrome – a case control study. BMC Oral Health 2012. **12**(17): p. 1-8.
35. Vedin O, H.E., Östlund O, et al., on behalf of the STABILITY Investigators. , Associations between tooth loss and prognostic biomarkers and the risk for cardiovascular events in patients with stable coronary heart disease. Int J Cardiol. , 2017. **245**: p. 271–6.
36. Hayder AA., M.M., AKS, Raghdan Z., and WHSA-D, Relationship of levels of transforming growth factorbeta1 (TGF-β1) to the levels of ferritin in blood of transfusion dependent β-thalassemia major patients with growth retardation: A case-control study. EurAsian J Biosci., 2020. **14**(1): p. 521-552.
37. Fouad D., A.J., Mohsin R. , Mousa MJ., Makki HA., BAA-K. , Possible cause-and-effect linkage of transforming growth factor-beta1 and platelets derived growth factor-AB with delayed anthropometric parameters in adolescent patients with Cooley's anemia: Cases vis control

research strategy. EurAsian J Biosci., 2020. **14**(1): p. 1119-1125.
38. Sun, W., Wu, Y., Gao, M., Tian, Y., Qi, P., Shen, Y., Huang, L., Shi, L., Wang, Y., & Liu X. , C-reactive protein promotes inflammation through TLR4/NF-κB/TGF-β pathway in HL-1 cells. Biosci Rep., 2019. **39**(8): p. BSR20190888.
39. Al-Hindy H., e.a., No Significant Relationship of Ferritin Levels to the Levels of Platelet-derived Growth Factor (PDGF) in the Peripheral Blood of Transfusion-dependent β- Thalassemia Major Patients with Growth Retardation. Int J Pharm Res. , 2020. **12**(3): p. 568-575.
40. Ho, K.J., Owens, C. D., Longo, T., Sui, X. X., Ifantides, C., & Conte MS. , C-reactive protein and vein graft disease: evidence for a direct effect on smooth muscle cell phenotype via modulation of PDGF receptor-beta. Am J Physiol Heart Circ Physiol. , 2008. **295**(3): p. H1132–H1140.
41. Galea, R., et al., Inflammation and C-reactive protein in atrial fibrillation: cause or effect? Texas Heart Institute journal, 2014. **41**(5): p. 461-468.