Kehinde A. Umeizudike
https://orcid.org/ 0000-0003-4893-872X
Janet N. Ajuluchukwu
https://orcid.org/ 0000-0002-1124-9763
Opeyemi A. Obilade
https://orcid.org/ 0000-0001-6409-4235
Azeez BUTALI
https://orcid.org/ 0000-0002-1229-5964

Citation: Alade GO, Ayanbadejo PO, Umeizudike KA, Ajuluchukwu JN, Obilade OA, Butali A. Effect of non-surgical periodontal therapy on C- reactive protein levels in hypertensive patients at a tertiary health institution in Nigeria. Nig J Periodontal Res 2022; 3(1):1-11.

CLINICAL IMPLICATIONS

C-reactive proteins have been linked to periodontitis, but the effect of periodontitis and non-surgical periodontal treatment on C-reactive protein among Nigerian hypertensive individuals is unknown. C-reactive protein levels were significantly reduced three months after non-surgical periodontal therapy. The effect of non-surgical periodontal therapy (scaling and root planing) on C-reactive protein levels may be beneficial in reducing systemic inflammatory burden in hypertensive patients. C-reactive protein monitoring is essential for hypertensive patient management, especially in those with periodontitis.

INTRODUCTION

Periodontitis is a chronic multifactorial inflammatory disease, associated with dysbiotic dental plaque biofilms, and is increasingly being linked to a number of systemic conditions.[1] The prevalence of periodontitis remains high and varies in different parts of the world, with a prevalence of 42.2% in the United States of America (mild to moderate periodontitis (34.3%), severe periodontitis (7.8%),[2] 73% in Germany and 53% in Iran.[3] In Nigeria, however, it was reported that the prevalence of periodontitis (shallow pocket depth of 4 - 5 mm) was 39 % among subjects who were 15 years of age; this increased to 57 % among those aged 25 -39 years but decreased to 17 % among those aged 65 years and older.[4] More recently, Umeizudike et al reported a periodontitis prevalence of 48.9% (both shallow (4-5 mm) and deep (≥6mm) pockets) in an adult urban population in Nigeria.[5]

Periodontitis results in irreversible, destruction of the tooth connective tissue attachment and alveolar bone leading to tooth loss if untreated.[6] The plaque biofilms harbour virulent bacteria such as *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans* and *Treponema denticola*. Not only do these periodontal microorganisms initiate inflammation within the periodontal tissues by activating the white blood cells (neutrophils) of the innate immune system, they also stimulate a robust destructive host inflammatory response, characterized by the release of cytokines including tumour necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 into the body system.[7] Thus, this inflammatory burden by periodontitis has linked it to many systemic diseases, such as rheumatoid arthritis,[8] aspiration pneumonia,[9] type 2 diabetes mellitus,[10] cancer,[11] and cardiovascular disease (CVD).[12]

Also, the systemic effects of periodontitis have been demonstrated by the release of acute-phase elements/reactants such as C-reactive protein (CRP), into the circulation.[13] C-reactive protein is produced mainly by the liver, with a serum range of 0-10mg/l, but elevated within 72 hours of tissue injury or infection.[14,15] It is an established independent predictor of cardiovascular disease (CVD)[16] and has been proposed by the American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC) as an inflammatory marker to assess the risk of cardiovascular disease more than a decade ago.[17] A decrease in high sensitivity (hs)-CRP levels has been reported following periodontal therapy in periodontitis patients who are at risk of cardiovascular disease.[18] Also, recently, a meta-analysis of the effect of periodontal therapy on the surrogate markers of cardiovascular diseases, reported reduction of low-grade inflammation as evaluated by the serum level of CRP, IL-6 and improvements in surrogate measures of endothelial function (flow-mediated dilatation of the brachial artery).[19]

Hypertension is the commonest risk factor for the emergence of several cardiovascular diseases such as coronary artery disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, etc.[20] The prevalence of hypertension could vary depending on the criteria and target population used to define it. The prevalence of hypertension among US adults from 2011-2014 was 45.6% using the new blood pressure thresholds from the 2017 American College of Cardiology/AHA guidelines and higher compared to 31.9% based on the guidelines from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[21] It is also the most prevalent non-communicable disease in Nigeria.[22] Ogah et al found the prevalence to be 8% - 46.4%, depending on the target population.[23] More recent prevalence rates among urban dwellers in Nigeria were reported as 55.0% and 27.5%, based on the ACC/AHA 2017 guideline and the JNC-7 2003 guidelines respectively.[24]

Hypertension has been linked to atherosclerosis; a chronic inflammatory condition [25] and the underlying pathogenesis for cardiovascular diseases such as coronary heart disease (CHD) and stroke, which constitute a public health problem globally and in Nigeria.[26] These account for an estimated 17·8 million deaths in 2017, of which more than three quarters were in low-income and middle-income countries (LMIC).[27] An association between periodontitis and cardiovascular disease have been reported by a number of epidemiological and clinical studies. [28,29] It has been proposed that periodontal bacteria such as Porphyromonas gingivitis, Tannerella forsythia or Treponema denticola are present in as high as 52% of atherosclerotic specimens.[30] Porphyromonas gingivalis was also identified in the coronary plaque of Coronary artery disease patients in a cohort study. [31]

Inflammation plays a critical role in the development of atherosclerotic lesions. [32] This is initiated by the alteration in the structure of the endothelium, leading to the expression of adhesion molecules, e.g., vascular adhesion molecules (VCAM), intercellular adhesion molecules (ICAM) and recruitment of immune cells such as macrophages into the arterial wall. Leukocytes, then bind to the endothelium, favouring lipid accumulation and the formation of chemokines, which in turn promote the build-up of smooth muscle cells.[33] As a result of inflammatory stimulation, secretion of metalloproteinases and rupture of the fibrous cap, occurs, causing plaque rupture and acute coronary syndrome. [33]

The beneficial effect of periodontal therapy on endothelial dysfunction in periodontitis subjects with systemic health or conditions such as hypertension has been documented [34] and may thus, reduce the risk of cardiovascular disease. [35] Regarding these effects, few studies have assessed the link between periodontitis and hypertension among Nigerians. A study found a significant association between self-reported hypertension and periodontitis in an adult population of administrative medical staff in Nigeria.[5] Long-term treatment of hypertension and its complications is not affordable to many patients in Nigeria.[36] This is because majority of Nigerians live in extreme poverty; below $1.90 a day [37] and most pay through out-of-pocket means. [38] In view of the high burden of hypertension and its co-morbidities in Nigeria, the need to explore non-traditional preventive measures to reduce hypertensive-associated complications, as well as the paucity of data on the link between periodontitis and cardiovascular disease in Nigerians, were the reasons why this study was undertaken. A preliminary study by the researchers had reported an association between elevated CRP levels and the severity of periodontitis among hypertensive patients in Nigeria.[39] The aim of the current study was to elucidate the effect of non-surgical periodontal therapy on the levels of CRP in individuals with hypertension in Nigeria.

MATERIALS AND METHODS

The present study was a prospective interventional study that was carried out at the Cardiology and Periodontology Clinics of the Lagos University Teaching Hospital (LUTH), Nigeria. Ethical approval was obtained from the Health Research and Ethics Committee (HREC) of the Lagos University Teaching Hospital, Idi-Araba, Lagos State (ADM/DCST/HREC/306). The study population consisted of 50 hypertensive subjects diagnosed with periodontitis, and 50 healthy controls. Hypertension was defined according to the JNC-7, as persistent blood pressure measurement with systolic/diastolic blood pressure values ≥140/90 mmHg or if a patient being treated with antihypertensive drugs, had been diagnosed by a consultant cardiologist.[40] The inclusion criteria were patients at least 18 years old, on antihypertensive medications, and had at least 20

natural standing teeth. Participants on periodontal tissue-modifying medications, inflammatory conditions (such as arthritis, gastrointestinal disorder), diabetes mellitus, pregnancy, and smokers were excluded from the study following a detailed history and clinical presentation.

Participants with hypertension were first screened using the Community periodontal index (CPI) [41] probe and classified into the hypertensives with periodontitis group (mean CPI score was 3.06 ± 0.24). Healthy volunteers with systemic and periodontal health (with mean CPI score of 0.88 ± 1.003) were included to serve as controls so as to define their CRP levels for baseline reference values in Nigerians.

Determination of Sample size

The sample size expression, $N = (Z_\alpha + Z_\beta)^2 * (\sigma_1^2 + \sigma_0^2) / (\delta)^2$ was used.

Where:n = required sample size for each group, Z_α and Z_β = the values of the standardized normal deviate corresponding to specified confidence and power levels and α =type 1error while β is type 11 error

σ_0^2 and σ_1^2 were the estimated variances of C-reactive proteins in the groups respectively. While δ was the desired minimum detectable difference between any two groups.

In this study, the level of confidence was specified at 95% and the power was fixed at 80%.

σ_0 = 1.9 i.e., standard deviation of C-reactive protein in the hypertensive group with periodontitis before treatment

σ_1 = 0.9 i.e., standard deviation of C-reactive protein in the hypertensive group with periodontitis after treatment.

Value of C-reactive protein in the hypertensive group with periodontitis before treatment = 2.7mg/l, while value of C-reactive protein in the hypertensive group with periodontitis after treatment = 1.8mg/l.[42]

δ was set at 0.9 (2.7-1.8).

$$N = \frac{(1.96 + 0.84)^2 \times (1.9^2 + 0.9^2)}{0.9^2}$$

$$N = \frac{(2.8)^2 \times (1.9^2 + 0.9^2)}{0.81}$$

N = 42.7 = 43 To give allowance for 10% attrition, the adjusted sample size was:

N=43/ (1-0.10) = 47

The required minimum sample size for each group was 47.

Clinical Periodontal Assessment

Periodontitis was classified into mild, moderate and severe, following a full mouth periodontal examination with the Williams periodontal probe. Mild periodontitis was characterized by two or more interproximal sites with attachment loss ≥ 3 mm and two or more interproximal sites with probing depths ≥ 4 mm, not on the same tooth, or one site with probing depth ≥ 5 mm, moderate periodontitis was characterized by two or more interproximal sites with attachment loss ≥ 4 mm, not on the same tooth, or two or more interproximal sites with probing depths ≥ 5 mm, not on the same tooth. Severe periodontitis was characterized by two or more interproximal sites with attachment loss ≥ 6 mm, not on the same tooth, and one or more interproximal sites with probing depth ≥ 5 mm.[43] Baseline periodontal indices evaluated include the clinical attachment loss (CAL), periodontal pocket depth (PPD), and bleeding on probing (BOP). All the clinical examinations were carried out by a single investigator. The intra-examiner's reliability was 0.8 using Kappa Statistics.

The baseline periodontal assessment, was followed by non-surgical periodontal therapy (NSPT) which consisted of scaling and root planing, alongside subgingival irrigation with normal saline alternated with 0.2% Chlorhexidine gluconate mouth rinse. Each subject received post-operative instructions and were placed on 0.2% Chlorhexidine gluconate mouth rinses 12 hourly for two weeks, systemic antibiotics (Amoxycillin 500mg 8hourly for five days in combination with Metronidazole 200mg 8hourly for five days or Doxycycline 200mg start, then 100mg daily for ten days for patient with allergies to Amoxycillin or Metronidazole). Assessment of the periodontal parameters, CAL, PPD, BOP, was repeated after three months, to evaluate the outcome of the nonsurgical periodontal therapy. Clinical attachment loss (CAL) was calculated from the summation of the periodontal probing depth (PPD) and gingival recession.

Blood sample collection

About 5mls of peripheral venous blood samples were collected from each participant, using a large-bore (18-22G) needle inserted into a vein in the antecubital fossa or dorsum of the hand. The blood samples were placed in plain tubes and transported within 30 minutes to the AIDS Prevention Initiative in Nigeria (APIN) laboratory at LUTH. Blood samples were

obtained prior to the NSPT (baseline) and three months after the NSPT for C-reactive protein analysis. The tubes containing blood samples were chilled promptly in an ice bath. Sera harvested from blood samples, were swiftly divided into aliquots and stored at -70˚C until the time of the assay. Serum concentration of C-reactive protein was measured using the Immunoturbidimetry method (Roche Hitachi C311 Auto-analyzer). The clear tubes containing the blood samples of the respective participants were coded to blind the laboratory scientist carrying out the C-reactive protein analysis.

Statistical analysis

Data analysis was done using the statistical package for social sciences (SPSS), by IBM® for Windows version 20.0. Descriptive summary statistics obtained for demographic variables and differences in proportion was tested using Chi-square at 95% confidence interval. The Independent T-test was used to compare the mean C-reactive protein levels between the hypertensive with chronic periodontitis group and the control group. The Paired T-test was used to compare the mean C-reactive protein levels in the hypertensive with chronic periodontitis group before and 3 months after treatment. P-value below 0.05 was considered to be statistically significant.

RESULTS

There were 50 hypertensive subjects with periodontitis (11 males and 39 females) and 50 controls (20 males and 30 females). (χ^2 =3.79, P = 0.052) The mean age of the cases was 52.4 ± 6.96 years, while the mean age of the controls was 50.12 ± 8.48 years. Many of the cases (38%) had secondary school education, while majority of the controls (50%) had tertiary education, as shown in Table 1.

Table 1: Sociodemographic characteristics of the Participants

Variable	Cases (%)	Control (%)	P value
Age group (years)			
30-39	1 (2.0)	7 (14.0)	
40-49	18 (36.0)	14 (28.0)	
50-59	23 (46.0)	24 (48.0)	0.165#
60-69	7 (14.0)	4 (8.0)	
70-79	1 (2.0)	1 (2.0)	
Total	50 (100.0)	50 (100.0)	
Gender			
Female	39 (78.0)	30 (60.0)	0.052
Male	11 (22.0)	20 (40.0)	
Total	50 (100.0)	50 (100.0)	
Education			
No formal education	3 (6.0)	0 (0.0)	
Primary	14 (28.0)	13 (26.0)	
Secondary	19 (38.0)	12 (24)	<0.001#
Tertiary	14 (28.0)	25 (50.0)	
Total	50 (100.0)	50 (100.0)	
Occupation			
Unemployed	3 (6.0)	1 (2.0)	
Self-employed	31 (62.0)	1 (2.0)	<0.001#
Private	3 (6.0)	3 (6.0)	
Civil Servant	13 (26.0)	45 (90.0)	
Total	50 (100.0)	50 (100.0)	

Fisher Exact p-value. *p* values below 0.05 are statistically significant at the 5% significance level

There was a significant reduction in the systolic blood pressure from baseline values (147.22 ± 19.69 mmHg) to 3 months after periodontal therapy (143.72 ±17.10 mmHg (P<0.001). There was also a significant reduction in the diastolic blood pressure from baseline (94.34 ± 14.66mmHg) to 3 months after periodontal therapy (87.68 ± 9.49 mmHg) (P<0.001)

among the subjects with hypertension. This is shown on Table 2.

There was a statistically significant reduction in mean periodontal pocket depth (P < 0.001), bleeding on probing (P < 0.001) and mean clinical attachment loss (P < 0.001) from baseline to three months after periodontal therapy (Table 3).

There was a statistically significant difference between the mean CRP level of the hypertensive subjects with periodontitis; 3.18 ± 2.93 mg/l and the mean CRP level of the periodontally healthy, non-hypertensive controls; 1.15 ± 0.73 mg/l (P < 0.0001), as shown on Table 4.

There was a statistically significant difference between the mean CRP level of the hypertensive subjects with periodontitis at baseline (3.18 ± 2.93 mg/L) and 3 months after periodontal therapy (1.66 ± 1.03 mg/L). (P<0.001). This is shown on figure 1. Also, the median CRP level of hypertensive subjects at baseline; [2.3(0.9, 4.4) mg/L], was statistically reduced at 3 months after periodontal therapy; [1.8(0.8, 2.4) mg/L]. (P < 0.001).

Table 2: Comparison of Blood pressure of hypertensive with periodontitis subjects at baseline and 3 months after periodontal therapy

Blood pressure (mmHg)	Baseline (mean ±SD	3 months after treatment (mean ±SD)	*P* value *
Systolic	147.22 ±19.69	143.72 ±17.10	<0.001
Diastolic	94.34 ±14.66	87.68 ± 9.49	<0.001

*Paired T test used for hypothesis testing. *p* values below 0.05 are statistically significant at the 5% significance level

Table 3: Comparison of Periodontal parameters of the hypertensive subjects with periodontitis before and after periodontal therapy.

Periodontal parameters	Baseline (mean ± SD)	3 months after treatment (mean ± SD)	P value*
Pocket depth	4.46 ± 0.93	0.66 ± 1.03	<0.001
Bleeding on probing	3.40 ± 3.26	0.58 ± 1.01	<0.001
Clinical attachment Loss	2.07 ± 2.66	1.25 ± 1.68	<0.001

*Paired T test used for hypothesis testing. *p* values below 0.05 are statistically significant at the 5% significance level

Table 4: C-reactive protein levels of the hypertensive subjects with periodontitis and the controls at baseline.

Group	Baseline CRP (mg/l)	P value*
Cases	3.18 ± 2.93	<0.001
Controls	1.15 ± 0.73	

*Independent T test used for hypothesis testing. *p* values below 0.05 are statistically significant at the 5% significance level.

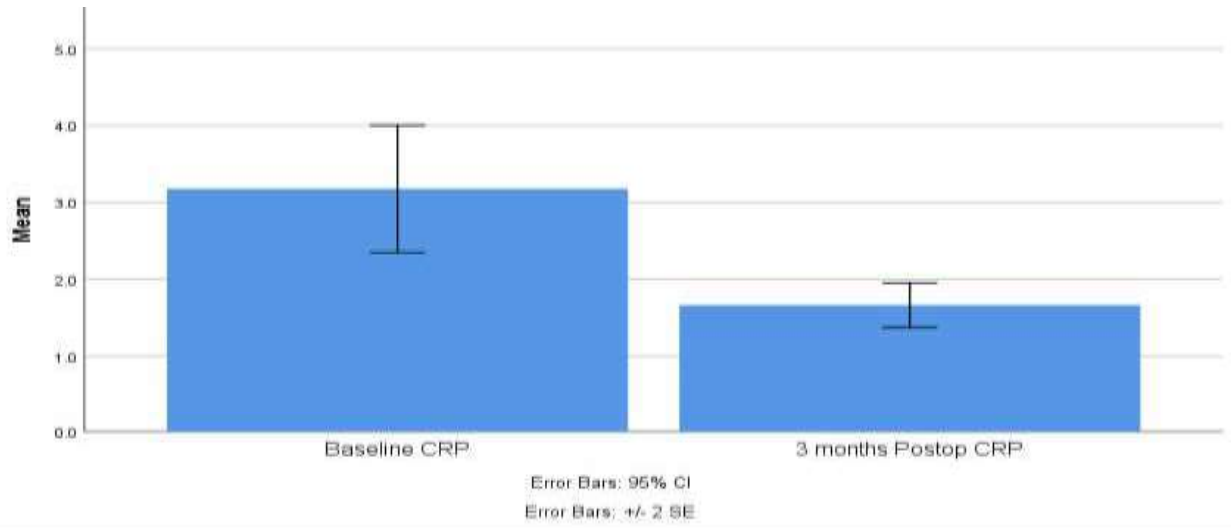

Figure 1: Bar chart of the mean CRP levels of the hypertensive subjects with periodontitis at baseline and three months after periodontal therapy

*Paired T test used for hypothesis testing. *p* values below 0.05 are statistically significant at the 5% significance level

DISCUSSION

Studies have documented the relationship between cardiovascular disease and periodontitis in Non-Nigerian populations.[19,44] The current study investigated the effect of non-surgical periodontal therapy on CRP levels in hypertensive subjects with periodontitis. To the best of our knowledge, this is the first study to report this among Nigerians with hypertension. The main findings of this prospective interventional study were the reduction in the severity of the periodontal indices and CRP levels three months following periodontal therapy in the patients. The older age group observed is however not surprising considering the documentation of increasing age as a risk factor for several systemic illnesses including hypertension [23] as well as periodontitis.[45] Older age was also associated with self-reported hypertension in non-medical staff of a health institution in Lagos, Nigeria who had periodontitis.[5]

In addition to the CPI which was initially used to screen the participants. The mean periodontal probing depth (PPD), percentage bleeding on probing (BoP) sites and mean clinical attachment loss (CAL) were the indices utilized in this study. They provided a comprehensive full mouth record of the periodontal status and were therefore employed, rather than the less sensitive partial mouth indices such as the CPI which was utilized in a study among hypertensive patients in Nigeria.[46] The significant reduction observed in the values of the mean periodontal probing depth and the gain in mean clinical attachment loss, between the baseline and three months after NSPT, is similar to the finding in a previous study.[47] Scaling and root planing (NSPT) is effective in reducing the bacterial load and altering their ecological niche through mechanical debridement, hence aiding reattachment of periodontal fibers, reduction in periodontal pocket depth and gaining of clinical attachment. There was also a reduction in the percentage bleeding on probing (BoP) from the baseline to three months after NSPT, this follows the trend in previous studies.[48,49] Bleeding on probing (BoP) is a parameter which is utilized in monitoring gingival health and gingival inflammation, [50] and is caused by the micro-ulceration of the gingival sulcular lining. It has been reported that absence of BoP signifies periodontal health,[51] hence, reduction of BoP from baseline to three months after NSPT indicates an improvement of the periodontal health of the hypertensive subjects.

The mean CRP of the control group in this present study is similar to that reported in a previous study among patients with acute ischaemic stroke,[52] also the statistically significant difference between the control group and the hypertensive subjects with periodontitis follows the trend of a previous study, [53] Thus, the mean CRP levels in the current study could therefore represent an important, unbiased baseline/reference value for the systemically healthy adult Nigerian population who do not have periodontitis.

The marked reduction in CRP levels following intervention by non-surgical periodontal therapy (scaling and root planing) among the hypertensive subjects in the current study has also been reported in a previous study. [53] This was further buttressed in the meta-analyses that highlighted the influence of periodontal therapy on the reduction of biomarkers including CRP in patients with cardiovascular disease.[54,55] C-reactive protein is an acute phase protein produced by the hepatocytes, and its production is regulated by interleukin-6 (IL-6), interleukin-1β (IL-1β) and Tumour necrosis factor-α (TNF-α); which are inflammatory mediators that are elevated during periodontitis. [56-58] This implies that treatment of periodontitis aimed at reducing the constant bacterial challenge to the host systemic immunity through mechanical root debridement could also mitigate systemic inflammation evidenced by lowered CRP levels. [59]

There was significant reduction in the blood pressure of the participants between baseline and at three months after periodontal therapy, this finding follows the trend of a previous study. [60] This reduction in systolic and diastolic blood pressure could be due to the reduction in inflammation after the non-surgical periodontal therapy and hence the repair of the endothelial lining and improvement of endothelial function. However, this finding should be interpreted with caution, as the subjects were also on antihypertensive drugs, which have also been reported to reduce the C-reactive protein levels. [61, 62]

Hypertension has been associated with atherosclerosis, which is a chronic inflammatory state.[32] Inflammation may contribute to a rise in blood pressure by promoting changes in the endothelial lining, with elevated levels of CRP inducing structural and functional changes in the endothelium, which ultimately contributes to the development of hypertension. Hence the marked reduction in CRP is attributed to the positive effect of periodontal treatment on chronic inflammation in hypertensive subjects with chronic periodontitis.
Limitations of the study include the small sample size. A prospective, multicentre study using a larger sample size should be considered to elucidate this preliminary finding among Nigerians.

CONCLUSION

This study showed that CRP is associated with periodontitis and that non-surgical periodontal therapy through subgingival scaling and root planing significantly reduces CRP levels in hypertensive patients. Periodontal therapy may therefore be beneficial in reducing cardiovascular events associated with elevated CRP levels in hypertensive patients. Therefore, the treatment of periodontitis through periodontal therapy may be an additional and essential means of managing hypertension in Nigerians, hence, reducing the risk of cardiovascular complications.

ACKNOWLEDGEMENTS

We are grateful to the Late Professor W.O Savage who contributed immensely to the concept, design and supervision of this study. We are also grateful to Mr. Tony Ani, who helped with the laboratory analysis of C-reactive protein samples.

Financial Sponsorship
No external source of funding

Conflict of Interest
None declared

REFERENCES

1. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: Consensus report of workgroup 2 of the 2017 world workshop on the classification of periodontal and peri-implant disease and conditions. 2018; 45(S20): S162-S170.
2. Eke P, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA, Genco RJ. Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009-2014. J Am Dent Assoc 2018; 149:576-588.e6.
3. Nazir M, Al-Ansari A, Al-Khalifa K, Alhareky M, Gaffar B, Amas K. Global prevalence of periodontal disease and lack of its surveillance. Sci World J 2020; doi.org/10.1155/2020/2146160.
4. Adegbembo AO, El-Nadeef MA. National study of periodontal status and treatment need among Nigerians. Int Dent J 1995; 45:197-203.
5. Umeizudike KA, Ayanbadejo PO, Onajole AT, Umeizudike TI, Alade GO. Periodontal status and its association with self-reported hypertension in non-medical health workers in a University Teaching Hospital in Nigeria. Trop Dent J 2016; 39:47-55.
6. Kurgan S, Kantarci A. Molecular basis for immunohistochemical and inflammatory changes during progression of gingivitis to periodontitis. Periodontol. 2000 2018; 76:51-67.
7. Andrukhov O, Ulm C, Reischi H, Nguyen PQ, Matejka M, Rausch-Fan X. Serum cytokine levels in periodontitis patients in relation to the bacterial load. J Periodontol 2011; 82: 885-892.
8. Lundberg K, Wegner N, Yucel-Lindberg T, Venables PJ. Periodontitis in RA—the citrullinated enolase connection. Nat Rev Rheumatol. 2010; 6:727-730.
9. Yamanishi T, Takao K, Koizumi H, Ishihama K, Nohara K, Komaki M, et al. Alpha2-adrenoceptors coordinate swallowing and respiration. J. Dent Res 2010; 89:258-263.
10. Zadik Y, Bechor R, Galor S, Levin L. Periodontal disease might be associated even with impaired fasting glucose. Br Dent J 2010; 208:E20
11. Tan KH, Seers CA, Dashper SG, Mitchell HL, Pyke JS, Meuric V. et al. *Porphyromonas gingivalis* and *Treponema denticola* exhibit metabolic symbioses. PLoS Pathog 2014; 10: e1003955.
12. Holmlund A, Lampa E, Lind L. Oral health and cardiovascular disease risk in a cohort of periodontitis patients. Atherosclerosis 2017; 262:101-106.
13. Loos BG. Systemic markers of inflammation in periodontitis. J Periodontol. 2005; 76:2106-2115.
14. Ojo DA, Jacob SJ, Ayolabi CI. C-reactive protein in tuberculosis and human Immunodeficiency

virus infection in Abeokuta, Nigeria. Bayero J Pure Appl Sci 2011; 4:91-96.
15. Bansal T, Pandey A, Deepa D, Asthana AK. C - reactive protein (CRP) and its Association with periodontal disease: A Brief review. J Clin Diagn 2014; 8:ZE21-ZE24.
16. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342:836 - 843.
17. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centres for Disease Control and Prevention and the American Heart Association. Circulation 2003; 107:499-511.
18. Samad R, Akbar FH, Willianto OA, Malinta QU, Namirah HA. Effect of scaling and root planing treatment on levels of Hs-CRP in Indonesian patients with risk of cardiovascular disease. Pesqui Bras Odontopediatria Clin Integr 2019; 19(1):02.doi.org/10.434/pboci.2019.191.02
19. Sanz M, Castillo AV, Jepsen S, Gonzalez-Juanatey JR, D'Aiuto F, Bouchard P, et al. Periodontitis and cardiovascular diseases: Consensus report. J Clin Periodontol 2019; 47:268-288.
20. Tackling G, Borhade MB. Hypertensive Heart disease. [Updated 2021 Feb 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan, 2021
21. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics—2019 Update: A Report from the American Heart Association. Circulation 2019; 139:e56-e528.
22. Akinkugbe OO. Non-Communicable Diseases in Nigeria—Final Report of a National Survey. Lagos: Federal ministry of health– national expert committee on NCD. Ibadan: Spectrum Books Limited (Publishers) 1997:1-12
23. Ogah SO, Okpechi I, Chukwuonye II, Akinyemi JO, Onwubere BJ, Falase AO. et al. Blood pressure, the prevalence of hypertension and hypertension-related complications in Nigerian Africans: A review. World J Cardiol 2012; 4:327-340.
24. Okubadejo NU, Ozoh OB, Ojo OO, Akinkugbe AO, Odeniyi IA, Adegoke OI. et al. Prevalence of hypertension and blood pressure profile among Urban-dwelling adults in Nigeria: a comparative analysis based on recent guideline recommendations. Clin Hypertens 2019; 25:7. doi:10.1186/s40885-019-0112-1.
25. Paoletti R, Gotto AM Jr, Hajjar DP. Inflammation in Atherosclerosis and implication for therapy. Circulation 2004; 109:111-20-111-26.
26. Ike SO, Onyema CT. Cardiovascular disease in Nigeria: What has happened in the past 20 years? Nig J Cardiol 2020; 17:21-27.
27. Roth GA, Abate D, Abate KH, Abay SM, Cristiana A, Abbasi, N. et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392:1736-1788.
28. Kebschull M, Demmer RT, Papapanou PN. "Gum bug, leave my heart alone!"—epidemiologic and mechanistic evidence linking periodontal infections and atherosclerosis. J Dent Res 2010; 89:879-902.
29. Mochari H, Grbic JT, Mosca L. Usefulness of self-reported periodontal disease to identify individuals with elevated inflammatory markers at risk of cardiovascular disease. Am. J. Cardiol 2008; 102:1509–1513.
30. Kurihara N, Inoue Y, Iwai T, Sugano N, Umeda M, Huang N, Ishikawa I. Oral bacteria are a possible risk factor for valvular incompetence in primary varicose veins. Eur. J. Vasc. Endovasc. Surg, 2007; 34: 102-106.
31. Chhibber-Goel J, Singhal V, Bhowmi D, Vivek R, Parakh, N, Bhargava B, et al. Linkages between oral commensal bacteria and atherosclerotic plaques in coronary artery disease patients. NPJ Biofilms Microbiomes 2016; 2:7.
32. Rosenfeld ME. Inflammation and atherosclerosis: direct versus indirect mechanisms. Curr Opin Pharmacol 2013; 13:154-160.
33. Rosenson R, Brewer H, Rader DJ. Lipoproteins as biomarkers and therapeutic targets in the setting of acute coronary syndrome. Circ Res 2014; 114: 1880-1889.
34. Sharma S, Sridhar S, McIntosh A, Messow C, Aguilera EM, Pinto RD, et al. Periodontal therapy and treatment of hypertension-

alternative to the pharmacological approach. A systematic review and meta-analysis. Pharmacol Res 2021; 166:105511.
35. Chugh SS. (2010) Early identification of risk factors for sudden cardiac death. Nat Rev Cardiol 2010; 7:318-326.
36. Okwuronu CG, Ojimodu NE, Okaka EI, Akermokwu FM. Patient-related barriers to hypertension control in a Nigerian population. Int J Gen Med 2014; 7:345-353.
37. World Bank Data Portal. Poverty & Equity Brief-Nigeria, October 2018.
38. Shogade TT, Akpabio AA. Insufficient control of blood pressure in the population of Nigeria and Africa. Eur Heart J.2019; 17:26
39. Alade GO, Ayanbadejo PO, Umeizudike KA, Ajuluchukwu JN. Association of Elevated C-Reactive Protein with Severe Periodontitis in Hypertensive Patients in Lagos, Nigeria: A Pilot Study. Contemp Clin Dent 2018; 9(Suppl 1): S95-S99.
40. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. http://hyper.ahajournals.org/content/42/6/1206.full
41. Patil VA, Desai MH. Effect of periodontal therapy on serum c-reactive protein levels in patients with gingivitis and chronic periodontitis: A clinicobiochemical study. J Contemp Dent Pract 2013;14(2):233-237
42. Higashi Y, Goto C, Hidaka T, Soga J, Nakamura S, Fujii Y, Hata T, Idei N, Fujimura N, Chayama K, Kihara Y, Taguchi A. Oral infection–inflammatory pathway, periodontitis, is a risk factor for endothelial dysfunction in patients with coronary artery disease. Atherosclerosis 2009; 206:604–610.
43. Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. J Periodontol 2007; 78:1387-1391.
44. Yang S, Zhao L, Cai C, Shi Q, Wen N, Xu J. Association between periodontitis and peripheral artery disease: A systematic review and meta-analysis. BMC Cardiovasc Disord 2018; 18:141.doi.org/10.1186/s12872-018-0879-0
45. Eke PI, Dye BA, Wei L, Thornton-Evans GO, Genco RJ. Prevalence of periodontitis in adults in the United States: 2009 and 2010. J Dent Res 2012; 91:914- 920.
46. Arowojolu MO, Oladapo O, Opeodu OI, Nwhator SO. An evaluation of the possible relationship between chronic periodontitis and hypertension. J West Afr Coll 2016; 6(2):20-38.
47. Choi YM, Lee J, Choi J, Joo J. Effect of root planing on the reduction of probing depth and the gain of clinical attachment depending on the mode of interproximal bone resorption. J Periodontal Implant Sci 2015; 45(5): 184-189.
48. Herrera D. (2016). Scaling and Root Planning is Recommended in the Nonsurgical Treatment of Chronic Periodontitis J. Evid. Based Dent. Pract, 2016; 16:56-58.
49. Krishna R, De Stefano JA. Ultrasonic vs. hand instrumentation in periodontal therapy: Clinical outcomes. Periodontol 2000. 2016; 71:113-127.
50. Lang NP, Joss A, Tonetti MS. Monitoring disease during supportive periodontal treatment by bleeding on probing. Periodontol 2000 1996; 12:44-48
51. Lang NP, Bartold PM. Periodontal health. J Clin Periodontol, 2018; 45(S20):S9-S16.
52. Abubakar SA, Okubadejo NU, Ojo OO, Oladipo O, Ojini FI, Danesi, MA. Relationship between admission serum C-reactive protein and short-term outcome following acute ishaemic stroke at a tertiary health institution in Nigeria. Niger J Clin Pract 2013;16:320-324.
53. Samad R, Akbar FH, Willianto OA, Malinta QU, Namirah HA. Effect of scaling and root planing treatment on levels of Hs-CRP in Indonesian patients with risk of cardiovascular disease. Pesqui. Bras. Odontopediatria Clin. Integr. 2019; 19(1):02:doi.org/10.434/pboci.2019.191.02.
54. Roca-Millan E, González-Navarro B, Sabater-Recolons MM, Marí-Roig A, Jané-Salas, E, López-López J. Periodontal treatment on patients with cardiovascular disease: Systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal 2018; 23 (6):e681-690.
55. Teeuw WJ, Slot DE, Susanto H, Gerde VE, Abbas F, D'Auito F, et al. Treatment of periodontitis improves the atherosclerotic profile: a systematic review and meta-analysis. J Clin Periodontol 2014; 41:70-79.
56. Gupta S, Gupta I, Gupta R, Gupta P. Role of C-reactive protein in periodontal disease – a review. Int J Contemp Med Res 2017; 4(5):980-985.
57. Bansal T, Pandey A, Deepa D, Asthana AK. C - reactive protein (CRP) and its Association with

periodontal disease: A Brief review. J Clin Diagn Res. 2014; 8:ZE21-ZE24.
58. Torrungruang K, Katudat D, Mahanonda R, Sritara P, Udomsak A. Periodontitis is associated with elevated serum levels of cardiac biomarkers-soluble ST2 and C-reactive protein. J Clin Periodontol 2019; 46: 809-818
59. Gupta S, Suri P, Patil PB, Rajguru JP, Gupta P, Patel N. Comparative evaluation of role of hs C - reactive protein as a diagnostic marker in chronic periodontitis patients. J Family Med Prim Care. 2020; 9:1340-1347
60. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski, D, et al. Casual association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. Eur Heart J 2019; 40 3459-3470.
61. Mahmood IH. The effects of captopril and amlodipine in c-reactive protein concentrations in type ii diabetic hypertensive patients. Pak J Med Sci, 2008; 24(4):485-490
62. Silva IVG, de Figueiredo RC, Rios DRA. Effect of different classes of antihypertensive drugs on endothelial function and inflammation. Int J Mol Sci 2019; 20(14):3458. doi.org/10.3390/ijms20143458