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Assessment of relationship between acute cerebrovascular stroke and periodontal disease: A Clinico-biochemical study

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Abstract
Background: The aim of this study is to assess the periodontal status of patients suffering from acute cerebrovascular ischemic stroke, to ascertain C-reactive protein, serum cholesterol and serum cortisol levels in patients with acute cerebrovascular ischemic stroke and to correlate it with clinical parameters.
Methods: The case control study consisted of 50 test group patients diagnosed with acute cerebrovascular stroke with neuroimaging and 50 healthy control patients. A detailed case history was recorded. Clinical parameters like plaque index, gingival index and probing pocket depth and biochemical parameters like c-reactive protein, serum cholesterol and serum cortisol levels were assessed. The values obtained were compared by statistical analysis using student's T- test and Pearsons' correlation.
Results: Plaque index, gingival index, probing pocket depth, C-reactive protein, serum cholesterol and serum cortisol levels were significantly higher in test group as compared to control group ($P \leq 0.001$). Significant positive correlation was observed between the clinical parameters and biochemical parameters.
Conclusion: Periodontal status was poorer in patients of test group as compared to control group. The biochemical parameters were notably higher in patients with test group as compared to control group. A significantly positive correlation was seen between test and control group.

Keywords: periodontal disease, acute cerebrovascular ischemic stroke, C-reactive protein, serum cholesterol, serum cortisol

Introduction
Periodontal disease is a multifactorial infectious process resulting from a complex interplay between chronic bacterial infection and the inflammatory host response, leading to destruction of tooth-supporting tissues which is irreversible and finally causes loss of tooth [1]. Association of periodontal infection with systemic conditions affecting cardiovascular and cerebrovascular system, endocrine system, reproductive system and respiratory system makes it a complex multiphase disease. Acute cerebrovascular ischemic stroke is the most important and frequently occurring neurological disease which causes an impairment of body functions that are controlled by the affected portion of the brain. Active periodontal inflammation contributes to a prothrombotic state by recurrent bacteremia, platelet activation, and elevated clotting factors, which increase the risk of acute cerebrovascular stroke [2]. Several studies have investigated the association between stroke and periodontal disease by evaluating the clinical parameters. To our knowledge, none of the studies have evaluated the relationship between stroke and periodontal disease correlating clinical parameters with biochemical parameters like C - reactive protein, serum cholesterol and serum cortisol till date. We have performed this case control study to assess this relationship correlating the clinical parameters and biochemical parameters.

Materials and Methods
Test group included 50 patients who were diagnosed with acute cerebrovascular ischemia from their case history and clinical examination and were admitted to the Department of Medicine, Department of Neurology and Neurosurgery, SMS medical college and hospital and were subjected to neuroimaging (CT Scan 128 tesla) which revealed an acute ischemic lesion and /or neurological deficit lasting for more than 24 hours [3]. Control group included 50 age matched patients selected from Department of Periodontology and Implantology, Jaipur Dental College who had no present or past history of acute cerebrovascular ischemic stroke and were systemically healthy.

Inclusion Criteria
- Patients diagnosed with acute cerebrovascular ischemic stroke by CT Scan (128 tesla) and hospitalized for same reason
- Both male and female patients were considered.
- Age : 35-70 years
- Examined within 5-7 days after their first attack of stroke.

Exclusion criteria

- Patients with a history of previous attack of stroke
- Patients diagnosed with hemorrhagic stroke on neuroimaging
- Patients who are completely edentulous
- Female patients who are pregnant or lactating
- Patients who have undergone any periodontal therapy in previous 12 months
- Patients who were unable to give informed consent
- Patients with any other known systemic disease.
- Patients on any known medication

Case History

Informed written consent was obtained from all patients or their blood relations/spouse. A detailed medical and dental history was recorded for every patient which included diet, family history, habits like smoking, alcohol intake, and tobacco. Patients in the control group were age matched with test group. Patients were also assessed for systemic conditions like diabetes, hypertension to rule out other risk factors for acute cerebrovascular stroke. Out of 587 patients examined, 50 patients without any history of systemic disease other than stroke were recruited for study in the test group.

Periodontal examination

The patients were subjected to a complete periodontal examination by the same clinician. Patients were examined in supine position with the help of a regular torch for illumination, a mouth mirror, a periodontal probe (UNC-15). Clinical parameters like Gingival Index: (Loe and Silness, 1963) [4], Plaque index: (Silness and Loe 1964) [4] and Probing pocket depth (using UNC 15 periodontal probe) [5] were assessed. Two milliliters of blood sample was withdrawn from anticubital fossa to assess biochemical parameters like C-Reactive protein [6], serum cholesterol [7] and serum cortisol [8]. The data obtained was subjected to statistical analysis.

Statistical analysis

Results of the following study were subjected to statistical analysis by applying Students' T Test and Pearson's correlation [9].

Results

The comparison between the clinical and the biochemical parameters was done between control group and the test group.

Control group

The mean (mean ± SD) plaque index, gingival index and probing pocket depth was calculated to be 0.81±0.13, 0.91± 0.10 and 3.86±0.70 respectively. The mean (mean ± SD) serum C - reactive protein level, serum cholesterol level and serum cortisol level was calculated to be 0.94± 0.24, 197.3± 22.8 and 15.35± 2.90 respectively (Table 1).

Test group

The mean (mean ± SD) plaque index, gingival index and probing pocket depth was calculated to be 1.20±0.15, 1.40±0.09 and 6.52±1.09 respectively. The mean (mean ± SD) serum C - reactive protein level, serum cholesterol level and serum cortisol level was calculated to be 6.90±1.41, 248.36 ± 34.62 and 24.17± 2.39 respectively (Table 1).

On correlation of plaque index, gingival index, probing pocket depth, c-reactive protein, serum cholesterol levels and serum cortisol levels of test and control group it was found to be more for test group which was statistically significant ($p \leq 0.001$)(Table 2). In the present study it was seen that males were more affected by acute cerebrovascular ischemic stroke as compared to females. Also it was seen that smokers, regular alcohol drinkers and non vegetarians were more affected with stroke. Results also showed that people having a family history of stroke were more affected with stroke than those with no family history. The difference was statistically significant. ($p \leq 0.001$)(Table 3).

Table 1: Statistical analysis of clinical and biochemical parameters using Students' T- Test

Plaque Index (PI)							
Variable	**Disease**	**N**	**Mean**	**Std Dev**	**Std Err**	**Minimum**	**Maximum**
PI	Control	50	0.81	0.1374	0.0194	0.6	1
PI	Test	50	1.206	0.1557	0.022	1	1.5
PI	Diff (1-2)		-0.396	0.1468	0.0294		
Variable			Method	Variances	DF	t Value	Pr > |t|
PI			Pooled	Equal	98	-13.48	<.0001
PI			Satterthwaite	Unequal	96.5	-13.48	<.0001
Gingival Index (GI)							
Variable	**Disease**	**N**	**Mean**	**Std Dev**	**Std Err**	**Minimum**	**Maximum**
GI	Control	50	0.916	0.1037	0.0147	0.7	1.2
GI	Test	50	1.408	0.0966	0.0137	1.2	1.6
GI	Diff (1-2)		-0.492	0.1002	0.02		
Variable			Method	Variances	DF	t Value	Pr > |t|
GI			Pooled	Equal	98	-24.55	<.0001
GI			Satterthwaite	Unequal	97.5	-24.55	<.0001

Probing Pocket Depth (PPD)							
Variable	**Disease**	**N**	**Mean**	**Std Dev**	**Std Err**	**Minimum**	**Maximum**
PPD	Control	50	3.86	0.7001	0.099	3	5
PPD	Test	50	6.52	1.0925	0.1545	5	8
PPD	Diff (1-2)		-2.66	0.9175	0.1835		
Variable			Method	Variances	DF	t Value	Pr > |t|
PPD			Pooled	Equal	98	-14.50	<.0001
PPD			Satterthwaite	Unequal	83.4	-14.50	<.0001
C-Reactive Protein (CRP)							
Variable	**Disease**	**N**	**Mean**	**Std Dev**	**Std Err**	**Minimum**	**Maximum**
CRP	Control	50	0.944	0.24	0.0339	0.5	1.5
CRP	Test	50	6.904	1.4155	0.2002	4	9.7
CRP	Diff (1-2)		-5.96	1.0152	0.203		
Variable			Method	Variances	DF	t Value	Pr > |t|
CRP			Pooled	Equal	98	-29.35	<.0001
CRP			Satterthwaite	Unequal	51.8	-29.35	<.0001
Serum Cholesterol							
Variable	**Disease**	**N**	**Mean**	**Std Dev**	**Std Err**	**Minimum**	**Maximum**
Cholesterol	Control	50	197.38	22.853	3.232	132	238
Cholesterol	Test	50	248.36	34.624	4.8965	190	301
Cholesterol	Diff (1-2)		-50.98	29.335	5.867		
Variable			Method	Variances	DF	t Value	Pr > |t|
Cholesterol			Pooled	Equal	98	-8.69	<.0001
Cholesterol			Satterthwaite	Unequal	84.9	-8.69	<.0001
Serum Cortisol							
Variable	**Disease**	**N**	**Mean**	**Std Dev**	**Std Err**	**Minimum**	**Maximum**
Cortisol	Control	50	15.354	2.9072	0.4111	6.7	20
Cortisol	Test	50	24.17	2.3678	0.3349	15.3	28.4
Cortisol	Diff (1-2)		-8.816	2.6513	0.5303		
Variable			Method	Variances	DF	t Value	Pr > |t|
Cortisol			Pooled	Equal	98	-16.63	<.0001
Cortisol			Satterthwaite	Unequal	94.1	-16.63	<.0001

Table 2: Correlation of clinical and biochemical parameters using Pearsons' correlation

Correlations							
		serum cortisol level (mcg/dl	**plaque index**	**gingival index**	**pocket probing depth**	**CRP levels**	**serum cholesterol level (mg/dl)**
serum cortisol level (mcg/dl	Pearson Correlation	1	.610(†)	.743(†)	.681(†)	.796(†)	.618(†)
	Sig. (2-tailed)		.000	.000	.000	.000	.000
plaque index	Pearson Correlation	.610(†)	1	.844(†)	.851(†)	.873(†)	.512(†)
	Sig. (2-tailed)	.000		.000	.000	.000	.000
gingival index	Pearson Correlation	.743(†)	.844(†)	1	.836(†)	.905(†)	.572(†)
	Sig. (2-tailed)	.000	.000		.000	.000	.000
pocket probing depth	Pearson Correlation	.681(†)	.851(†)	.836(†)	1	.910(†)	.572(†)
	Sig. (2-tailed)	.000	.000	.000		.000	.000
CRP levels	Pearson Correlation	.796(†)	.873(†)	.905(†)	.910(†)	1	.627(†)
	Sig. (2-tailed)	.000	.000	.000	.000		.000
serum cholesterol level (mg/dl)	Pearson Correlation	.618(†)	.512(†)	.572(†)	.572(†)	.627(†)	1
	Sig. (2-tailed)	.000	.000	.000	.000	.000	

† Correlation is significant at the 0.01 level (2-tailed).

Table 3: Comparison of the variables assessed

Variables	Cases	Controls	Chi Square Value	p Value
Age	**42.59±3.97**	**42.53±4.47**	**0.567**	**0.4061[a]**
Gender				
Females	5	16	7.2936	0.0197†[b]
Males	45	34		
Smoking[1]				
Never	8	22	10.794	0.00453†[b]
Ex-Smoker	12	12		
Current	30	16		
Alcohol[1]				
Never	13	32	14.653	0.000658†[b]
Occasional	9	5		
Regular	28	13		
Family History				
Positive	32	13	14.5859	0.0001†[b]
Negative	18	37		
Diet				
Vegetarian	17	32	9.0036	0.0027†[b]
Non-Vegetarian	**33**	18		

†Statistically Significant
a Student's t-Test
b Chi Squared Test

Discussion

Periodontal diseases constitute one of the most common infections in the world. Its initiation and progression is influenced by a wide variety of determinants and factors, including subject characteristics, social and behavioral factors, systemic factors, genetic factors, tooth level factors, microbial composition of dental plaque and other emerging factors [10]. Periodontitis are associated with elevated markers of inflammation which are also an important risk factor for stroke. Studies done by Joshipura *et al*. 2003 [11], Grau *et al*. 2004 [3], and Beck at al 1996 [12] have proved a significant association between periodontal disease and risk of acute cerebrovascular ischemia. The first National Health and Nutrition Examination Survey (2000) further showed that periodontal diseases are one of the risk factors of non-hemorrhagic stroke [13]. Although various studies have assessed the relationship between acute cerebrovascular ischemic stroke and periodontal disease, the present study is the first study assessing this relationship using both clinical and biochemical parameters and correlating them in order to achieve a more significant relationship between the two. To ascertain a definite correlation between stroke and periodontal disease, we have included only those patients without any known systemic disease other than stroke, as both conditions are well known to be associated with major risk factors like hypertension and diabetes.

In the present study, we assessed the relationship between acute cerebrovascular stroke and periodontal disease using clinical and biochemical parameters. Periodontal examination of patients in test group revealed that the mean values of clinical parameters like plaque index, gingival index and probing pocket depth were significantly higher than that of control group patients ($p \leq 0.001$). The results of this study are in accordance with the study conducted by Dorfer *et al*. 2004 [14] which assessed the associations of different periodontal parameters with cerebral ischemia and found out that patients with stroke had higher clinical attachment loss than the control population. Pradeep *et al*. 2010 [15] also conducted a study to assess the relationship between periodontal disease and cerebrovascular stroke in which the values of mean plaque index, gingival index and probing pocket depth of subjects with cerebrovascular stroke were significantly higher when those compared to control group. Nader Abolfazli *et al*. 2011 [16] investigated the association of periodontal disease with cerebral ischemia and concluded that patients had higher loss of attachment than controls. Periodontal disease is a chronic inflammatory disease with periods of acute exacerbations and quiescence and its association with cerebral ischemia have been largely attributed to atherogenesis, atherosclerosis and complications of atherosclerosis. Bone loss and attachment loss which frequently occur in periodontal disease may precede cerebral ischemia as it takes a long time to develop. Oral microorganisms including periodontal pathogens enter the blood stream during transient bacteremia and play an important role in the development and progression of atherosclerosis leading to stroke [1]. Deshpande *et al*. 1998 [17] reported that organisms such as Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis and Tanerella forsythia interact with neutrophil and monocyte T cell axis to elicit an acute and chronic inflammatory response. These results provide indirect evidence for a causal role of periodontitis in pathogenesis of atherosclerosis.

In the test group the mean C- reactive protein level was significantly higher than control group ($p \leq 0.001$). This was in accordance with study done by J. David Curb 2003 [18] who assessed the relation between C-reactive protein levels and stroke and found out that C-reactive protein quartile increased over time to a 3.8-fold excess in patients with stroke. Balwant Rai 2009 [19] in his study also found that C - reactive protein was raised significantly in periodontitis patients as compared to controls. Elevated levels of C-reactive protein are related to higher risk of myocardial infarction, stroke, periodontal disease and peripheral vascular disease. Inflammation contributes to the progression of cardiovascular and cerebrovascular disease because inflammatory cells cause local weakening of atherosclerotic plaques, leading to rupture and thrombus formation. Moreover, C-reactive protein induces monocyte to express tissue factor, the initiator of the extrinsic pathway of coagulation, which further stimulates vascular thrombosis [20].

In the present study the mean serum cholesterol levels of patients in the test group was significantly higher than the control group ($p \leq 0.001$) which is in accordance with study done by Loesche *et al.* 2000 [21] in which they concluded that serum levels of total cholesterol, triglyceride and LDL were higher in patients with periodontal disease compared with those in the control group. Cui R *et al.* 2013 [22] also studied the association between cerebrovascular stroke and serum cholesterol levels and found out that excess risk of ischemic stroke was observed in men with higher serum total cholesterol levels than the control group. In contrast the study done by Tom Skyhøj Olsen 2007 [23] investigated the relation between total serum cholesterol and both stroke severity and post stroke mortality and concluded that a higher cholesterol level favors development of minor strokes. Abnormal cholesterol levels are strongly associated with cardiovascular

and cerebrovascular disease because these promote atherosclerosis which leads to systemic diseases like myocardial infarction, stroke, and peripheral vascular disease. Lipopolysaccharide acts as a systemic trigger that activates a cascade of inflammatory cytokines eliciting most of the vascular and coagulation complications associated with atherosclerosis.

In the present study, the mean serum cortisol level for the test group was found to higher than control group. O'Neill *et al.* (1991) [24] studied the relation of reactive hyperglycemia, stress, hormone response, and outcome in twenty three consecutive elderly patients after acute stroke attack and found that serum cortisol levels were significantly higher in patients with acute cerebrovascular stroke. Croucher *et al*. (1997) [25] also investigated the role of life events in periodontitis wherein he concluded that psychosocial factors and oral health risk behaviors cluster together as important determinants of periodontitis. Stress causes an immediate and marked increase in adrenocorticotropic hormone secretion from the anterior pituitary gland followed by an increased secretion of cortisol from the adrenal cortex which decreases the permeability of the capillaries thereby increasing the blood viscosity. It also causes inhibition of immune response and thus giving rise to increased susceptibility to infections like periodontal disease [26].

On correlating biochemical parameters with the clinical parameters in the test and control group, a significant positive correlation was found. Hence in the present study it was seen that the patients in test group had poorer periodontal status and elevated biochemical tests level as compared to control group. The foundation of the association between periodontal disease and other systemic inflammatory conditions is chronic inflammation, and individuals with periodontitis have greater risk of presenting endothelial dysfunction and cerebrovascular diseases. Therefore, the pathogeny of destructive periodontal disease and atherosclerotic disease can be related through common inflammatory cascade which has a direct effect on elevated biochemical parameters [2].

Periodontal disease and acute cerebrovascular stroke share common risk factors like diabetes, hypertension, hyperlipidemia, smoking, alcohol intake. In our study, the test group included patients who gave no history of any other systemic disease other than stroke. In the study done by Sylvan Lavy 1973 [27] they found out that only 42 % of the patients had hypertension and only 20% of the patients had diabetes out of all the patients assessed for risk factors like diabetes and hypertension. This means that hypertension and diabetes are important risk factors for occurrence of stroke but may not necessarily be present in all individuals. Other risk factors may also be involved or sometimes multiple risk factors can play a role in causing stroke.

In the course of our study the other risk factors responsible for causing stroke and periodontal disease were also assessed which include age, gender, family history, diet, smoking, and alcohol.

In the present study it was seen that males (66%) were more affected by acute cerebrovascular ischemic stroke as compared to females (34%) which was in accordance with the study done by Ralph L. Sacco (1997) [28]. Also, those people having a family history of stroke were more affected with stroke than those with no family history as suggested by Welin L (1987) [29] and Kiely DK (1993) [30]. In the present study non vegetarians were more affected with stroke as compared to vegetarians. Yvonne Bachmann in 2012 [31] and I Staufenbiel (2013) [32] concluded that vegetarians had significantly lower probing pocket depths, bleeding on probing, and periodontal screening index scores, better oral hygiene index scores and fewer mobile teeth. It was also seen that smokers were more affected with stroke than nonsmokers. This was not in accordance with study conducted by Hillbom *et al*. (1995) [33] but goes in hand with the study done by Preber *et al*. in 1980 [34] and Pradeep *et al*. (2010) [15] who found that people with smoking habits were more prone to develop stroke. In the present study it was seen that regular alcohol drinkers were more affected with stroke as compared to those who do not drink alcohol regularly. This was not in accordance with the study done by Pradeep *et al*. (2010) [15] whereas Hillbom *et al*. (1995) [33] concluded that alcohol is a significant risk factor for stroke.

Conclusion

This study reveals a significant difference between test and control group in clinical and biochemical parameters. Hence we conclude that periodontal status was poorer in patients of test group as compared to control group with higher biochemical parameters in test group. When the biochemical parameters were correlated with clinical parameters a significantly positive correlation was seen in the test and control group.

Periodontal disease and atherosclerosis have complex etiologies and risk factors and also share same pathogenic mechanisms. It is becoming increasingly clear that infections and chronic inflammatory conditions such as periodontitis may influence the atherosclerotic process. They increase haemostatic variable which form haemostatic plugs and thrombi, both of which play important roles in pathogenesis of vascular disease. Future research using larger sample size, detailed study regarding various types of stroke and other risk factors associated with stroke and to associate it with periodontal parameters would help us to better understand the relationship between periodontal disease and acute cerebrovascular ischemic stroke, and also improve its treatment outcome.

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