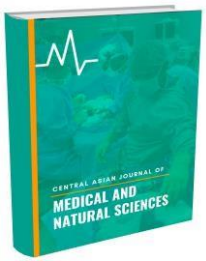

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Article

Estimation of Serum Level of Neurokinin A in Patients with Periodontitis in Association with Chronic Migraine Disease (Observational Case Control Study)

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Abstract: Recently, a relationship was found between periodontitis and chronic migraine. However, there is no evidence of the association between periodontitis and Neurokinin A (NKA) level in chronic migraine patients. As a result, we aimed to measure and compare serum levels of NKA in study and control groups in order to determine whether periodontitis is associated with chronic migraine disease activation. Eightytwo (82) males and females above the age of 18 were recruited. Subjects were divided into four groups: 27 patients with chronic migraine and periodontitis, 27 patients with chronic migraine and clinically healthy periodontium, 20 patients systemically healthy with periodontitis and eight subjects with clinically healthy periodontium and without any systemic disease. Assessment of periodontal status was carried out for all participants. Socio demographic data and comorbidities were assessed by means of a standard questionnaire then blood samples were collected and serum concentrations were separated for NKA. The serum level of NKA were higher in the control group (38±40) and there was a significant difference between the other groups when compared to the control group (P=0.003) and there was a weak negative significant correlation between neurokinin A and clinical periodontal parameters (BOP, Cal, and PPD) between all study groups. According to the findings of this study, the control group had a higher level of serum NKA. As a result, this peptide could be considered an indicator of disease severity and activity for both periodontitis and chronic migraine diseases. So far, no research has backed up our findings. Longitudinal studies are required to validate our findings.

Keywords: Periodontitis, Chronic Migraine, Neurokinin A (NKA), Neuropeptides, BOP

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1. Introduction

Migraine is a type of primary chronic headache described by recurring episodes of incapacitating and intense headaches that are typically pulsatile and unilateral, and symptoms such as nausea, vomiting, and hypersensitivity to light and noise (Ameijeira et al., 2019). This disease affects more than 11% of the general population, with a less prevalence in men (6%) than in women (18%) (Lipton et al., 2007). There are two forms of migraines: episodic and chronic. The major complication in episodic migraine is the chronicity of the disease, with progression at a rate of 3% per year (Scher et al., 2003).

Neurokinin A (also known as substance K) is a neuropeptide neurotransmitter that belongs to the tachykinin family. Nociceptive absorption and smooth muscle contraction

are all assisted by tachykinins. In the major central nervous systems, tachykinins are believed to be strongly excitatory neurotransmitters (Schäffer and Gábriel, 2005). The role of NKA in connecting nociceptive information refers to its potential relationship in the pathophysiology of pain and possibly vascular changes during migraine attacks. It has been postulated that NKA requires intact endothelium in order to relax precontracted cerebral arteries (Jansen et al, 1990).

After dental caries, periodontitis is the second most common oral infectious disease that affects the periodontium. It is caused by an inflammatory reaction triggered by the accumulation of bacterial plaque at the gingival edge of the tooth (Hughes, 2015). Periodontitis is characterized by the stimulation of osteoclastogenesis and the consequent permanent destruction of alveolar bone, which results in loss of tooth support (Könönen et al., 2019).

2. Materials and Methods

The present study was a self-funded case control (observational) study that started from January 2021 until June 2021. The subjects enrolled in the study were attendants seeking treatment in the neuromedicine in Al Zahraa Teaching Hospital; the patients were seeking periodontal treatment in the Al-kut dental specialized center. All the individuals were informed about the purpose of the current study. The medical and dental histories of the subjects were recorded by means of a questionnaire.

Eighty-two (82) subjects, were recruited in the present study. A pilot study was done to estimate the sample size. Subjects were divided into four groups as follow: 27 patients with chronic migraine and periodontitis, 27 patients with chronic migraine and clinically healthy periodontium, twenty patients systemically healthy with periodontitis and eight subjects with clinically healthy periodontium and apparently without any systemic disease. The subject with clinically healthy intact periodontium were selected according to criteria proposed by (Dietrich et al., 2019), periodontitis patients was defined according to criteria of (Tonetti et al., 2018). While for patient with chronic migraine disease, neurological examination was performed by a senior neurologist. according to the International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society, 2013).

Exclusion criteria were individuals with systemic conditions, extensive periodontal therapy or being currently under active periodontal treatment. Patients receiving antibiotic treatment or immunosuppressant medication within the last 3 months, pregnant or lactating mothers, with symptoms of recent acute illness, e.g., COVID-19, excluded as well.

Assessment of periodontal status was carried out for all participants by using a Michigan O periodontal probe. Six areas of each tooth were examined to assess gingival condition and the loss of periodontal support. Scores were given according to the criteria of the bleeding on probing (BOP), probing pocket depth (PPD) and clinical attachment loss (CAL) (Savage et al., 2009). Inter and intra examiner calibration were done with expert periodontitis until they reach 75% agreement for all clinical parameters.

After completion of periodontal examination, Fasted samples were collected in the morning at a painless interval at least twelve hours from the last migraine attack. Participants had not used any analgesic or anti-inflammatory medicine in the preceding 72 hours. Participants had not consumed anti-inflammatory or analgesic medication in the previous 72 hours. five ml of venous blood was collected from each then transferred into separating tubes, centrifuged for 15 minutes at (3000 rpm), and sera was separated, before being la-

beled and stored at (-80°C) for later analysis by the Enzyme Linked Immuno-Sorbent Assay (ELISA) for quantitative determination of serum level of NKA following manufacturer's instructions.

Finally, the statistical analysis for the present data were processed and analyzed using SPSS 21. Both descriptive and inferential analyses were used to accept or reject the statistical hypothesis. After using both of Kolmogorov-Smirnov and wilk Shapiro test to test the normality of distribution. For continuous variables, standard deviations and mean values were calculated. Categorical data were reported as percentages (%) and compared by X2 test. Non-normally distributed variables were tested by Kruskal Wallis test to compare the mean and medians values of biomarkers among groups. Furthermore, Bonferroni posthoc tests were employed for numerous connections across groups. The Spearman rank correlation coefficient was used to perform non-parametric correlation analysis between clinical periodontal measures and biomarkers in chronic migraine patients. Multivariate logistic regression analysis of variables association with disease status was done to investigate the significance association with disease. All tests were performed at a significance level of $\alpha = 0.05$.

3. Results

Concerning the mean BMI across chronic migraine with periodontitis, chronic migraine, periodontitis, and control group were 24.4 ± 3.5, 24 ± 3.3, 30 ± 3.6, and 22.3 ± 2.2 respectively as shown in (Table 1).

Table 1. BMI distribution across studied groups

		Mean	Standard Deviation
Group	1CM+P	24.43	3.54
	2CM	24.07	3.36
	3P	30.03	3.63
	4C	22.30	2.25

($P<0.05$). CM+P = chronic migraine with periodontitis, CM = chronic migraine with healthy periodontium, P = periodontitis, C = control

Statistical analysis using Independent Sample Kruskal-Wallis test showed that the mean BMI of periodontitis group was significantly higher in comparison to other groups as presented in (Figure 1).

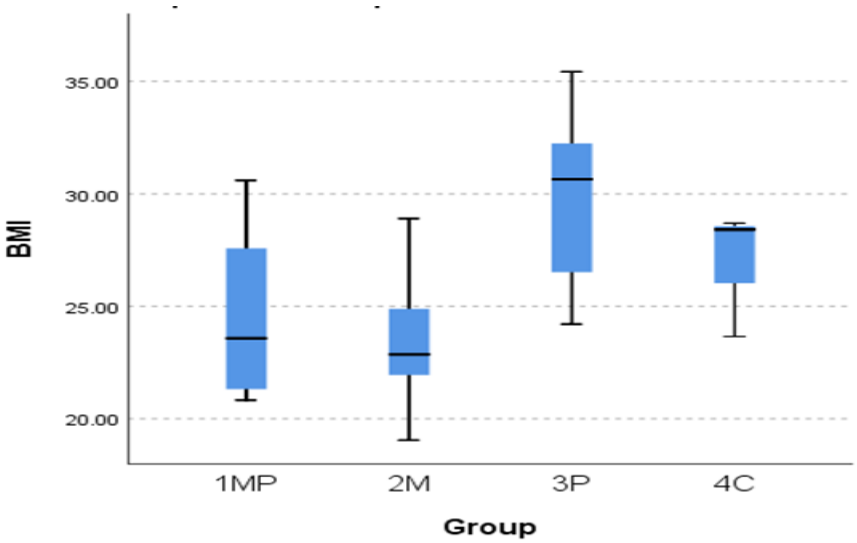

Figure 1. Mean BMI distribution across studied groups

Regarding the family history of migraine, majority of patients on migraine group were with positive family history of migraine (63%) and it was significantly higher in comparison to other groups (p=0.0001) (Table 2). Majority of participants in chronic migraine with periodontitis and chronic migraine with healthy periodontium groups were unemployed, while majority were employed among participants of periodontitis and control groups (Table 3). The distribution of employment status was not equally distributed across studied groups (P=0.016), with significant difference between migraine groups and periodontitis and control groups.

Table 2. Distribution of family history of migraine across studied groups

			Family History For chronic migraine		Total
			No	Yes	
Group	1CM+P	Count	22	5	27
		% within Group	81.5%	18.5%	100.0%
	2CM	Count	10	17	27
		% within Group	37.0%	63.0%	100.0%
	3P	Count	20	0	20
		% within Group	100.0%	0.0%	100.0%
	4C	Count	8	0	8
		% within Group	100.0%	0.0%	100.0%
Total		Count	60	22	82
		% within Group	73.2%	26.8%	100.0%

CM+P = chronic migraine with periodontitis, CM = chronic migraine with healthy periodontium, P = periodontitis, C = control

Table 3. Distribution of employment status across studied groups

			Educational Level		Total
			employee	unemployed	
Group	1CM+P	Count	7	20	27
		% within Group	25.9%	74.1%	100.0%
	2CM	Count	11	16	27
		% within Group	40.7%	59.3%	100.0%
	3P	Count	13	7	20
		% within Group	65.0%	35.0%	100.0%
	4C	Count	6	2	8
		% within Group	75.0%	25.0%	100.0%
Total		Count	37	45	82
		% within Group	45.1%	54.9%	100.0%

CM+P = chronic migraine with periodontitis, CM = chronic migraine with healthy periodontium, P = periodontitis, C = control

The present study illustrates that NKA was significantly higher among the control group in comparison to other groups. As its median was 37.75 pg/ml in controls while it was (7, 10, and 7) pg/ml in all study groups (Table 4). Table 5 shown that the results were based on two-sided tests assuming equal variances and there was significant difference between each study group in comparison with healthy controls, while there was non-significant difference in between study groups.

Table 4. Distribution of mean and median of NKA peptides across studied groups

Variable	**CM+P (A)**		**Migraine (B)**		**Periodontitis (C)**		**Control (D)**		**P value**
NKA	7±3	7	11±5	10	8±2	7	38±40	37.75	**0.003**

Table 5. Comparisons of column [a] of Inflammatory vasodilator peptides

	Groups			
	1MP	2M	3P	4C
	(A)	(B)	(C)	(D)
NKA	D	D	D	ABC

a. Tests are adjusted for all pairwise comparisons within a row of each innermost sub-table using the Bonferroni correction.

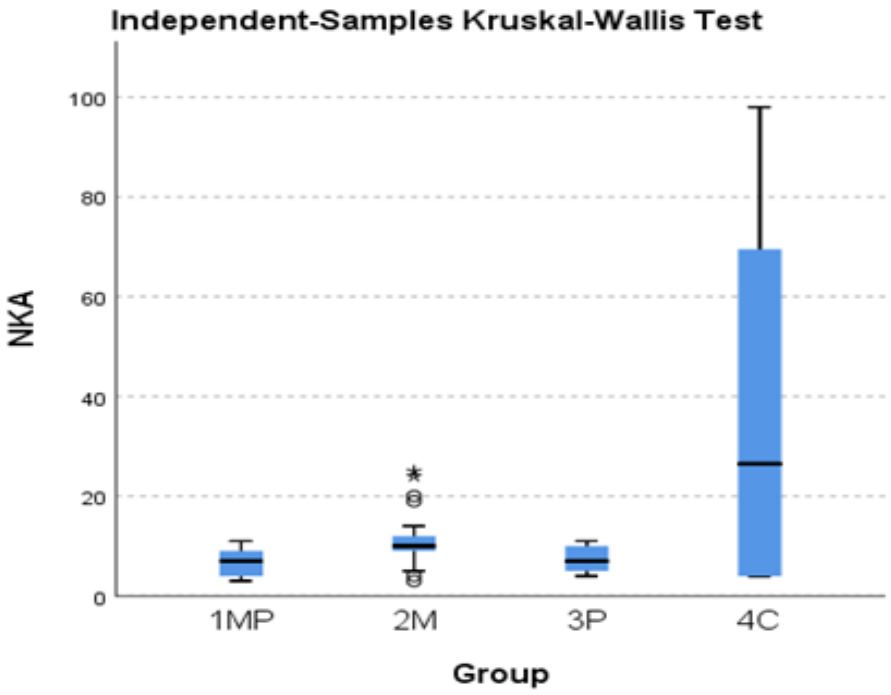

Figure 2. Comparisons of NKA levels among groups

The correlation between NKA and clinical periodontal parameters showed that there was a weak negative significant correlation between NKA and BOP, Cal, and PPD (Figure 3).

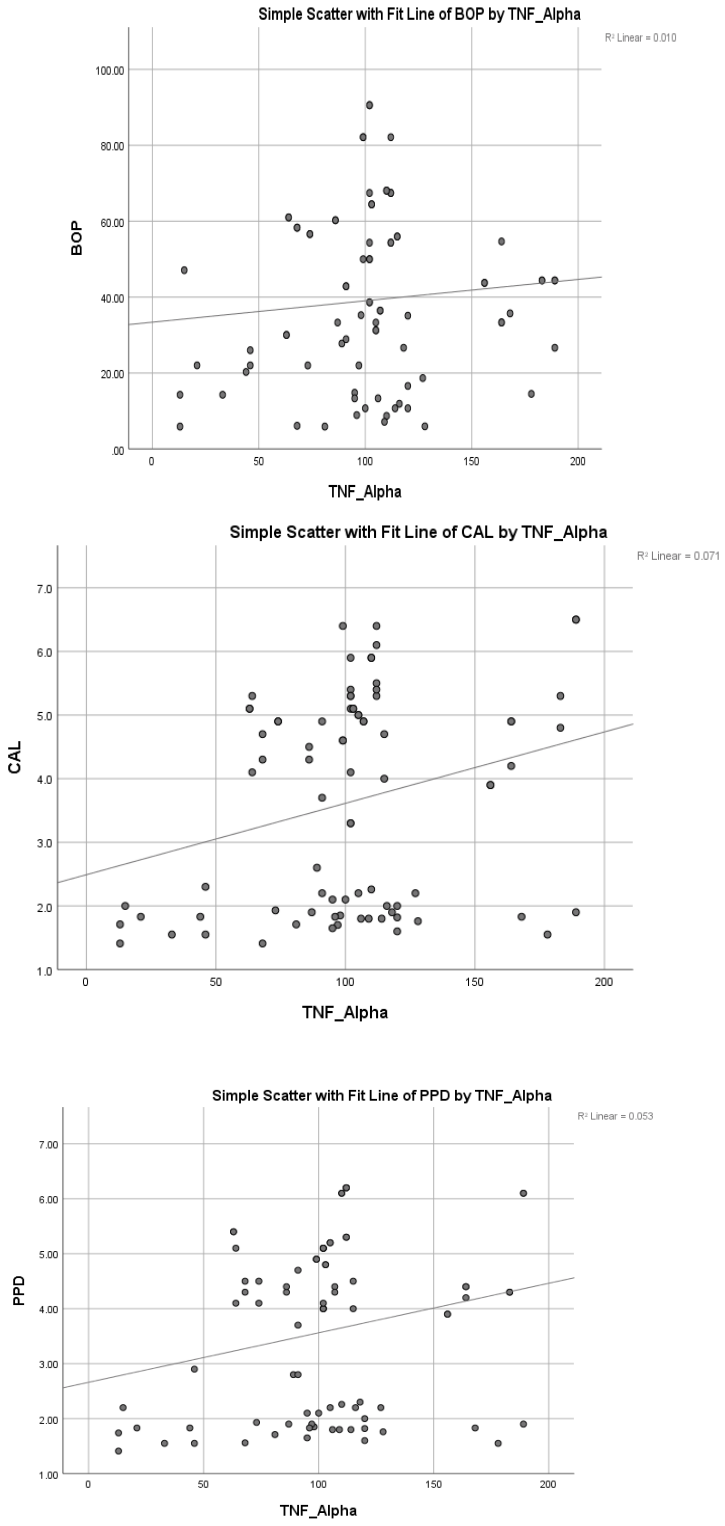

Figure 3. Correlation between TNF-α and clinical periodontal parameters. A; Correlation between TNF-a and CAL, P=0.36, r=-0.1. B; Correlation between TNF-α and POB, P=0.015, r=-0.26. C; Correlation between TNF-α and PPD, P=0.038, r=-0.23

4. Discussion

The relationship between periodontitis and migraine disease has become a topic of interest in the world. Clinical measures of periodontitis have been found to show an association with migraine disease and importance is now being placed on understanding the mechanism of interaction between periodontal disease and chronic migraine.

The present study showed that the mean of BMI was within the normal range (which is 18.5 to 24.9) in the control and chronic migraine groups. While BMI in periodontitis group was significantly higher (30.03 ±3.63) in comparison to other study groups. Obesity is a chronic metabolic condition that increases the risk of developing a number of comorbidities, including arterial hypertension, type 2 diabetes, atherosclerosis, and cardiovascular disease (Pischon et al., 2007). Obesity has also been suggested as a risk factor for periodontitis (Dahiya et al., 2012). Although the physiological and pathological mechanism is uncertain, it has been proposed that the emergence of insulin resistance as a result of long-term inflammation and oxidative stress may play a role in the obesity-periodontitis association (Martinez-Herrera et al., 2017).

Majority of participants in the chronic migraine with periodontitis and chronic migraine with healthy periodontium groups were unemployed. These findings agreed with (Buse et al., 2010) who reported that Patients suffering from chronic migraine had low household income and are much less prone to be full-time employed, and were more likely to be incapacitated in their occupation. Li and co-workers also found that in participants with migraine, there was a tendency for fewer years of education (Li et al., 2011).

The high frequency of migraines in unemployed participants may be related to the fact that low education is linked to low socioeconomic status, and the link between the two and migraine could be due to a variety of factors, including stress, an unhealthy lifestyle, and so on. In conclusion, the lower level of education is most probably a consequence of migraine (Li et al., 2011).

Regarding the family history of migraine, the majority of patients in the migraine group had a positive family history of migraine (63%) and it was significantly higher in comparison to other groups. This is consistent with previous research, which found a significant incidence of positive family history among migraine patients (Almalki et al., 2018)

Furthermore, the findings of a study conducted by Wieser et al revealed suggestive evidence for a migraine susceptibility locus on Xp22, which is responsible for a positive family history of migraine (Wieser et al., 2010). It was believed that having even one affected parent is a clear sign of possible inherited genetic characteristics that may make an individual more prone to migraine attacks.

The present result illustrated that high serum levels of NKA in the control group with significant difference in comparison with other study groups. These findings contradict those of (Liinden et al., 1997), who discovered higher levels of NKA in periodontal disease or gingivitis sites compared to healthy sites, and (Sert et al., 2019), who discovered an increase in SP and NKA levels in periodontitis/periimplantitis, gingivitis/peri-implant mucositis, and healthy periodontium/peri-implant groups. (Fujii et al., 2003) also stated that the levels of these two neuropeptides (SP and NKA) were observed to be higher in the GCF of individuals with periodontal diseases when compared with healthy people.

Neurokinin A has received little attention in the headache field so far. It is also found in the trigeminal system (Edvinsson et al., 1988) and is a less strong vasodilator than CGRP. The present study reported that the serum level of NKA decreased in the chronic migraine group compared to healthy controls.

According to the findings of this study, the control group had a higher level of serum NKA. As a result, this peptide could be considered an indicator of disease severity and activity for both periodontitis and chronic migraine diseases. So far, no research has backed up our findings.

5. Conclusion

The increased level of serum NKA in the control group when compared to other study groups suggests a role for NKA as a neuropeptide in both chronic migraine and periodontitis. Furthermore, there was a weak negative significant correlation between NKA and all clinical periodontal parameters that might suggest a direct association with disease severity and activity.

Limitations: The most important limitation is age and sex were matched for the periodontitis group and migraine with periodontitis only because of difficulty in finding the exact criteria among patients and limited time of sampling (not more than 6 months). Indeed, the present study is a case control study that show association but not the causality.

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