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The Expression of Biomarker Resistin in Both the Gingival Crevicular Fluid (GCF) and Serum of Patients with Chronic Periodontitis and Pacemaker Therapy: (A Clinical Study)

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Abstract

Background: Resistin is firstly introduced in 2001, as a cysteine-rich protein which is released from activated circulating monocytes together with those present inside the adipose tissues. It has been related to obesity and insulin resistance in animal models. Recently, elevated levels of serum resistin and Gingival crevicular fluid (GCF) is used as a biomarker for multiple inflammatory conditions. Chronic periodontitis is defined as a chronic inflammatory disease resulting from the accumulation of plaque, which leads to bacterial invasion of the immune defense mechanism and thus takes place in the pathogenesis of a systemic disease. Pacemaker patients are considered high-risk patients that require special care to prevent infection and failure of implantation of the device.

Subjects and Methods: This study included 60 subjects divided into four groups. Group I: patients with pacemaker therapy with a history of complications and re-implantation of the device, together with chronic periodontitis. Group II: Patients with chronic periodontitis only (medically free). Group III: Patients with chronic periodontitis with pacemaker device without previous complications or removal of the device. Group IV: Healthy individuals (Healthy periodontium and medically free). Levels of GCF and Serum resistin were measured in all four groups.

Results: There was a statistically significant difference between GCF Resistin values in the four groups (P-value <0.001), where groups I and III showed the highest levels followed by group II, whereas group IV showed the least GCF levels. Also, the high levels of GCF were statistically related to high median scores of plaque index(PI), modified gingival index(GI), and probing depth (PD) in groups I, II, and III respectively. There was a statistically significant difference in serum resistin levels and Groups I, III, II and IV respectively (P-value < 0.001). Also, there was a statistically significant co-relation between both Serum and GCF resistin values.

Conclusion: Elevated levels of both GCF and serum Resistin can play a critical role in detecting the level of inflammation, severity together with the prognosis of chronic periodontitis. They can be used to predict the presence of infection that may lead to future complications to the implanted pacemaker devices and hence affecting the lifestyle of this sort of patient.

Keywords: Adipokines, Resistin, Serum, Gingival Crevicular Fluid (GCF) Chronic Periodontitis, Pacemaker Therapy

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Introduction:

Periodontitis is considered a prevalent subclinical inflammatory disease which results from the accumulation of bacterial biofilm on the tooth surface. The plaque biofilm and its byproduct lead to the initiation of the host immune- inflammatory response. This response against the existing microorganisms has a dual effect; that is, an attempt to eliminate the infection, together with the destruction of local connective tissue and bone through the process of release of several pro-inflammatory mediators[1,2]. Several pro-inflammatory mediators such as interleukin 1(IL1), IL6, Tumor necrosis factor α (TNFα), prostaglandins E2(PGE2) are considered important biomarkers of periodontal diseases as well as great indicators of their activity[3].

These mediators also initiate neutrophils activation, leading to the release of a vast amount of matrix metalloproteinases (MMPS), and receptor activator of NF-κB ligand (RANKL), these destructive biochemicals lead to both collagen degradation together with bone resorption, and eventually tooth loss[4]. Therefore, the severity of any periodontal disease depends on the level of marginal bone loss, clinical attachment levels, periodontal pocket depths, and the number of teeth with furcation involvement in each quadrant[5]. This type of low-grade inflammation as chronic periodontitis can be the main factor in the pathogenesis and development of systemic disease[6].

Pacemaker therapy has been reported to be received by 300,000 patients in the United States each year, and about 900,000 devices worldwide. Pacemaker implantation is indicated in several conditions, e.g., bradyarrhythmias, certain types of syncope, congestive heart failure, and symptomatic bradycardia. Bradycardia has been reported to be associated with multiple symptoms as fatigue, lowered physical activity and obvious congestive heart failure. Pacemaker devices are usually implanted permanently to treat acquired atrioventricular block, dysfunction of the sinus node together with specific cases that require synchrony between the increased atrial contraction in relation to ventricular filling especially in old adults[7].

Congestive heart failure is a fatal condition that resulted in multiple morbidity rates during the last few decades. It causes myocardial hypertrophy, together with a disturbance in the neurohormonal system affecting the balance between the sympathetic and parasympathetic tone together with the disturbance in the renin-angiotensin-aldosterone system[8]. The inflammatory process plays an important role in heart failure cases not only through the myocardial damage but also through the release of inflammatory mediators that contribute to worsening of the heart failure condition[9].

Adipokines are a group of bioactive substances secreted mainly from adipose tissues, macrophages, and endothelial cells. Adipokines also include a group of classical cytokines, e.g., IL-1, IL-6, and TNFα. These biologically active substances include Adiponectin, Leptin, Visfatin, and Resistin. They also take place in the regulation of host inflammatory response, insulin sensitivity, and vascular function[10].

Resistin was first discovered in 2001, during a study that examined adipocyte differentiation genes[11]. It is a cysteine-rich secretory hormone that is 12.5 kDa and consisting of 108 amino acids. It also has a regulatory role in inflammation. Resistin is released from macrophages, neutrophils, and monocytes that exist both outside and within the human's adipose tissues. Its secretion is stimulated by IL-1, TNFα, IL-6 together with bacterial lipopolysaccharide (LPS) and its effect is mediated through NF-κB signaling pathway[12]. Recently, a study was done to determine the levels of resistin in the gingival crevicular fluid (GCF) of chronic periodontitis patients and showed that resistin was higher in chronic periodontitis patients when compared to healthy ones[13].

In 2013, Zimmermann et al. studied the levels of resistin and adiponectin in GCF and serum of both obese and normal weight individuals, with and without periodontitis. The results showed higher levels of resistin and lower levels of adiponectin in obese chronic periodontitis patients than in normal weight individuals with healthy periodontium[14]. Another study was carried out to determine the relation between cardiovascular diseases (CVD), and resistin; indicated that resistin participated in the aggravation of atherosclerosis through the activation polymorphonuclear leukocytes (PMNLs), endothelial cells, and vascular smooth muscle cells to initiate vascular inflammation[15].

In the last few years, attempts were established to highlight the basis of the pathogenic mechanism that binds cardiovascular diseases (CVD) to periodontal disease. These studies included the fact that inflammatory mediators from periodontal infections led to the atheroma plaque formation resulting in (CVD)[16]. Also, several studies have shown increased resistin levels related to other chronic inflammatory diseases such as diabetic retinopathy, rheumatoid arthritis, chronic kidney diseases and behçet disease[17].

According to the previously mentioned data, resistin is considered a novel and a major biomarker that is related to a wide range of inflammatory diseases. In this study, we tried to find the relation between levels of resistin in both serum and GCF in patients with chronic periodontitis and those with pacemaker devices. These patients are considered to be high-risk patients with infections following their device implantation. In addition to whether their periodontal condition affected their general health and the integrity of the implanted devices and comparing all these findings to serum and GCF resistin levels in healthy subjects.

Subjects and methods:

This study was performed after the approval of the Research Ethics Committee in Faculty of Dentistry, Cairo University with code number 17101. All participants were given an informed idea about the aim of the study and signed a consent form. Complete Blood Count (CBC) were done to healthy controls as a regular check-up and for the maximum benefit of their blood samples.

Patients selection:

Patients in this study were selected according to

Inclusion Criteria: Young adults, males, and females of age >30 years.

Exclusion Criteria: Patients suffering from any metabolic diseases like diabetes, and obesity, patients with chronic inflammatory diseases like Lichen planus, patients with immunologic diseases like systemic lupus, smoking patients, patients taking any medications especially lipid decreasing drugs.

Individuals in this study were recruited from the diagnostic center in Faculty of Dentistry, Cairo University. Patients with pacemaker therapy were selected from the outpatient's clinic of both Cardiology Department and Critical Care Center (Sherif Mokhtar ICU) Faculty of Medicine, Cairo University.

Study Design:

This study included 60 patients divided into four groups; each group included 15 patients. These groups were divided as follows:

Group I: Patients with pacemaker therapy with a history of complications and re-implantation of the device, together with chronic periodontitis.

Group II: Patients with chronic periodontitis only (medically free).

Group III: Patients with chronic periodontitis with pacemaker device without previous complications or removal of the device.

Group IV: Healthy individuals (Healthy periodontium and medically free).

- A single periodontist was responsible for the selection of chronic periodontitis patients. Groups I, II and III were selected as followed: Plaque index (PI) > 1, modified gingival index (GI) > 1, and probing depth (PD) ≥ 5 m.m. in more than four teeth in each quadrant. Also, panoramic radiographs were taken to confirm alveolar bone loss. Healthy participants had PI and GI ≤ 1 and probing depth ranging from 2-3 m.m

- Pacemaker patients were selected according to their records and were recommended as possible candidates for the study, by their follow- up consultants.

Gingival Crevicular Fluid (GCF) Collection:

The selected tooth was well isolated with a cotton roll; the supra-gingival plaque was removed with a curette. The cervical site; usually the one with the deepest probing depth score was gently dried with an air syringe. GCF was collected by placing a filter paper into the pocket until a blanching in the tissues was seen, then it was placed for 30 seconds. All the collected GCF samples were stored at a temperature -20ºC until evaluation. Contaminated strips with saliva or blood were excluded from the sample.

Serum Collection:

A venous blood sample was taken from each patient. The blood samples were centrifuged to obtain serum. All collected serum samples were also stored at temperature not less than -20ºC until further use. Quantitative assessment of resistin in both GCF and Serum was carried out by the commercially available ELISA Kit " Resistin (human) ELISA Kit, AdipoGen, Incheon, South Korea" for all the four groups according to the manufacturer's instructions. All samples were diluted by using the kit's diluent, A microtiter plate was used, and its wells were precoated with specific monoclonal antibody followed by pipetting of the samples into the wells to bind to the antibody. Incubation of the samples at 37ºC was done for one hour followed by extensive washing of the unbound compounds. The addition of the antibody, incubation at 37ºC for one hour, and the removal of excess unbound compounds are carried out again twice. After final washing, a substrate was added at room temperature. Stop solution was then added for 20 minutes to control the reaction. A color reaction was then produced; whose intensity depends directly on the resistin concentration in the samples.

Statistical Analysis:

Numerical data were explored for normality by checking the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). Age data showed normal (parametric) distribution while serum Resistin, GCF Resistin, Plaque Index (PI), Gingival Index (GI) as well as Pocket Depth (PD) data showed non-normal (non-parametric distribution). Parametric data were presented as mean and standard deviation (SD) values while non-parametric data were presented as median and Inter-Quartile Range (IQR) values. For parametric data; one-way ANOVA followed by Tukey's post-hoc test were used to compare between age values in the four groups. For non-parametric data; Kruskal-Wallis test was used to compare between the four groups. Dunn's test was used for pair-wise comparisons when Kruskal-Wallis test is significant. Qualitative data (Gender) was presented as frequencies and percentages. Chi-square test was used to compare between the four groups.

The significance level was set at P ≤ 0.05. Statistical analysis was performed with SPSS® Statistics Version 20 (NY, IBM®)for Windows.

Results:

Demographic data:

The mean and standard deviation values of age were 48.8 (8.8), 38.6 (8), 46.9 (10.7) and 31.6 (1.9) years old for Groups I, II, III and IV, respectively. There was a statistically significant difference between mean age values of the four groups (P-value <0.001). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between Group I and Group III; both showed the statistically significantly highest mean age values. There was no statistically significant difference between Group II and Group IV; both showed the statistically significantly lowest mean age values.

Group I comprised 8 males (53.3%) and 7 females (46.7%), Group II comprised 6 males (40%) and 9 females (60%), Group III comprised 8 males (53.3%) and 7 females (46.7%) while Group IV comprised 6 males (40%) and 9 females (60%). There was no statistically significant difference between gender distributions in the four groups (P-value = 0.784).

GCF Resistin:

Kruskal-Wallis test showed that there was a statistically significant difference between GCF Resistin values in the four groups (P-value <0.001). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between Group I and Group III; both showed the statistically significantly highest median GCF Resistin values. Group II showed statistically significantly lower value. Group IV showed the statistically significantly lowest median GCF Resistin value.

Serum Resistin:

Kruskal-Wallis test showed that there was a statistically significant difference between serum Resistin values in the four groups (P-value <0.001). Pair-wise comparisons between the groups revealed that Group I showed the statistically significantly highest median serum Resistin. Group III showed statistically significantly lower value followed by Group II. Group IV showed the statistically significantly lowest median serum Resistin value.

Plaque Index (PI)

Kruskal-Wallis test showed that there was a statistically significant difference between PI scores in the four groups (P-value <0.001). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between Group I, Group II and Group III; all showed the statistically significantly highest median PI scores. Group IV showed the statistically significantly lowest median PI score.

Gingival Index (GI)

Kruskal-Wallis test showed that there was a statistically significant difference between GI scores in the four groups (P-value <0.001). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between Group I, Group II and Group III; all showed the statistically significantly highest median GI scores. Group IV showed the statistically significantly lowest median GI score.

Probing Depth (PD)

Kruskal-Wallis test showed that there was a statistically significant difference between PD values in the four groups (P-value <0.001). Pair-wise comparisons between the groups revealed that there was no statistically significant difference between Group I and Group III; both showed the statistically significantly highest median PD values. Group II showed statistically significantly lower value. Group IV showed the statistically significantly lowest median PD value.

Outcomes	Group I (n = 15)		Group II (n = 15)		Group III (n = 15)		Group IV (n = 15)		*P*-value
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Serum Resistin (ng/µl)	410 ^{A}	310 - 510	180 ^{C}	165 - 210	325 ^{B}	270 - 460	35 ^{D}	18 - 45	<0.001*
GCF Resistin (ng/µl)	280 ^{A}	240 – 340	105 ^{B}	95 - 120	280 ^{A}	250 - 305	16 ^{C}	14 - 20	<0.001*
Plaque Index (PI)	3 ^{A}	3 - 3	2 ^{A}	2 - 2	2 ^{A}	2 - 3	0 ^{B}	0 - 0	<0.001*
Gingival Index (GI)	2 ^{A}	2 - 2	2 ^{A}	2 - 2	2 ^{A}	2 - 2	0 ^{B}	0 - 0	<0.001*
Pocket depth (mm)	7.5 ^{A}	7 – 8	5.5 ^{B}	5 - 6	7 ^{A}	6.5 – 7.5	1.5 ^{C}	1.5 - 2	<0.001*

Table 1. Descriptive statistics and results of Kruskal-Wallis test for comparison between different outcomes in the four groups

*: Significant at P ≤ 0.05, Different superscripts in the same row are statistically significantly different

Correlation between different outcomes

Group I: there was a statistically significant direct correlation between serum Resistin and GCF Resistin (P-value = 0.002) indicating that an increase in serum Resistin is associated with an increase in GCF Resistin and vice versa.

There was a statistically significant direct correlation between serum Resistin and Plaque Index (P-value = 0.019) indicating that an increase in PI is associated with an increase in serum Resistin and vice versa.

There was a statistically significant direct correlation between serum Resistin and Pocket Depth (P-value = 0.003) indicating that an increase in PD is associated with an increase in serum Resistin and vice versa.

There was a statistically significant direct correlation between GCF Resistin and age (P-value = 0.015) indicating that an increase in age is associated with an increase in GCF Resistin and vice versa.

There was a statistically significant direct correlation between GCF Resistin and Plaque Index (P-value = 0.019) indicating that an increase in PI is associated with an increase in GCF Resistin and vice versa.

Group II: there was a statistically significant direct correlation between serum Resistin and GCF Resistin (P-value <0.001) indicating that an increase in serum Resistin is associated with an increase in GCF Resistin and vice versa.

There was a statistically significant direct correlation between GCF Resistin and Pocket Depth (P-value = 0.007) indicating that an increase in PD is associated with an increase in GCF Resistin and vice versa.

Group III: there was a statistically significant direct correlation between serum Resistin and GCF Resistin (P-value = 0.006) indicating that an increase in serum Resistin is associated with an increase in GCF Resistin and vice versa.

There was a statistically significant direct correlation between serum Resistin and Plaque Index (P-value = 0.002) indicating that an increase in PI is associated with an increase in serum Resistin and vice versa.

There was a statistically significant direct correlation between serum Resistin and Pocket Depth (P-value <0.001) indicating that an increase in PD is associated with an increase in serum Resistin and vice versa.

There was a statistically significant direct correlation between GCF Resistin and Plaque Index (P-value = 0.017) indicating that an increase in PI is associated with an increase in GCF Resistin and vice versa.

There was a statistically significant direct correlation between GCF Resistin and Pocket Depth (P-value = 0.001) indicating that an increase in PD is associated with an increase in GCF Resistin and vice versa.

Group IV: there was a statistically significant direct correlation between serum Resistin and age (P-value <0.001) indicating that an increase in age is associated with an increase in serum Resistin and vice versa.

There was a statistically significant direct correlation between serum Resistin and Pocket Depth (P-value = 0.009) indicating that an increase in PD is associated with an increase in serum Resistin and vice versa.

Correlations with Plaque Index (PI) and Gingival Index (GI) were not computed for this group because all scores of PI and GI are zero.

Table 2. Results of Spearman's correlation coefficient for the correlation between serum, GCF Resistin, and different outcomes.

Outcomes	Group I (n = 15)	Group II (n = 15)		Group III (n = 15)		Group IV (n = 15)	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
Serum Resistin & Age	0.293	0.289	-0.100	0.723	-0.440	0.101	0.789	<0.001*
Serum Resistin & GCF Resistin	0.738	0.002*	0.900	<0.001*	0.673	0.006*	0.342	0.212
Serum Resistin & & PI	0.595	0.019*	0.000	1.000	0.731	0.002*	NC**	
Serum Resistin & GI	-0.031	0.912	-0.378	0.165	-0.156	0.579	NC**	
Serum Resistin & PD	0.704	0.003*	0.410	0.129	0.979	<0.001*	0.649	0.009*
GCF Resistin & Age	0.615	0.015*	-0.300	0.277	0.178	0.525	-0.132	0.640
GCF Resistin & & PI	0.595	0.019*	0.354	0.196	0.604	0.017*	NC**	
GCF Resistin & GI	-0.281	0.311	-0.378	0.165	-0.031	0.912	NC**	
GCF Resistin & PD	0.334	0.223	0.667	0.007*	0.767	0.001*	0.108	0.701

Table 2. Results of Spearman's correlation coefficient for the correlation between serum, GCF Resistin, and different outcomes.

*: Significant at P ≤ 0.05, NC**: Not Computed because all PI and GI scores are constant

Discussion:

Pacemakers are devices that are used for the treatment and prevention of various types of, disturbances in the cardiac rhythm [18]. The number of implanted devices has increased in the United States by 42% between 1990-1999[19]. In spite of the widespread use of these devices, few studies were concerned with the follow-up and the principal causes of the complications that followed their implantation. Also, there were no studies that related the relation between the periodontal condition and this sort of cardiac condition patients.

The goal of this clinical research is to study the relation between both GCF and Serum Resistin levels in both patients with pacemaker devices and chronic periodontitis. Also the study included a group of patients that experienced previous complications with their devices and required their removal and re-implantation of other devices. 28 males and 32 females patients participated in the study. There was no statistical significance difference between gender distributions in the four groups (P-value = 0.784).

After analyzing the GCF levels in all four groups; Group I and Group III; both showed the statistically significantly highest median GCF Resistin values. Group II showed statistically significantly lower value. Group IV showed the statistically significantly lowest median GCF Resistin value (P-value <0.001). These results agreed with Lockhart et al., in 2012 [20]; where their studies found a tight correlation between arteriosclerotic vascular diseases (also known as cardiovascular diseases) and periodontitis. This relation has been explained by the fact that both diseases are multifactorial, and periodontitis; being a source of chronic inflammation, can play an important role in the atheroma formation [20].

Also, there was a statistically significant difference between the scores of PI, GI and PD and GCF resistin (P- values <0.001). Group IV showed the statistically significantly lowest median scores while groups I, III, II showed higher significantly higher median scores respectively. These results were similar to those studies conducted by, Gonçalves el al. in 2015 [21], and Patel and Raju in 2014 [22], which stated that periodontal pockets with pocket depth ≥ 5 m.m. are considered to be inflammatory sites and had more GCF resistin levels than healthy controls. In 2008, Furugen et al[23]. also related sites with bleeding on probing to increased GCF resistin levels.

In this study, we also measured the serum resistin levels in all four groups. Group I showed the statistically significantly highest median serum Resistin. Group III showed statistically significantly lower value followed by Group II. Group IV showed the statistically significantly lowest median serum Resistin value (P-value <0.001). These results came similar to a study conducted by Takeishi et al. in 2007; where there was an increase in serum resistin levels in patients with cardiovascular diseases [24]. Furugen et al. [10], also related the increase in serum resistin levels and periodontitis to the fact that inflammatory mediators like IL-6, TNF-α, and resistin are released by the peripheral monocytes as a result of bacterial infections.

On comparing both the GCF resistin and serum resistin levels, Groups I, and III showed the higher levels, and they were statistically directly correlated to the high median scores (PI, GI, PD). This also confirms that the expression of resistin can be related to a group of inflammatory diseases and its degree of concentration in the samples can also predict the severity and prognosis of these diseases.

This study was the first to consider pacemaker patients as high-risk patients and try to deal with the fact that several factors can increase the risk of infection of the implanted device and cause its removal. Such factors include diabetes mellitus, malignancy, corticosteroids use, anticoagulant, and the most distinct factor is bacteremia from a promote focus of infection [25]. Since chronic periodontitis is considered a chronic inflammatory disease that creates a level of the subclinical systemic inflammation and act as a source of bacterial infection; this encouraged us to conduct this study among those high-risk patients.

In 2006, Dick et al. studied the role of resistin in coronary vasomotor

function; and found that resistin impairs bradykinin-induced relaxation of the coronary rings in vitro, thus plays an intricate role in the control of neovascularization together with vascular tone [26]. Several studies also related resistin to thrombus formation through its creation of a pro-thrombotic condition via the activation of NFκB transcription factor [27].

Based on all these facts; we chose the biomarker resistin to try to have a better understanding on whether or not the severity of periodontitis can play a huge role in maintaining the efficiency of pacemakers and preventing any complications which are considered morbid and thus affecting the life quality of those patients.

Our study had some limitations like the sample size was relatively small. Also, it had to include pacemaker patients with healthy periodontium, but that was challenging because most of the patients were weak, debilitated, and couldn't provide for the adequate dental or periodontal care.

Conclusion:

GCF and serum resistin is a newly distinguished biomarker that can reach its highest levels in patients suffering from chronic periodontitis and with pacemaker devices; especially those who experienced complications with their devices that required removal and re-implantation of new devices. The concentration of resistin can be used as a predictor of the severity and prognosis of certain inflammatory diseases.

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