

## Salivary profile and periodontal condition in patients with heart disease under warfarin treatment

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### Abstract

Heart disease is the leading cause of death in many countries. It refers to many conditions can be categorized into: electrical, circulatory and structural disorders. Warfarin drug is widely used anticoagulant medication for treatment of thrombosis and embolism. Patients on warfarin treatment are susceptible to bleeding and cannot perform oral hygiene practice properly therefore, periodontal diseases are commonly seen in those patients.

The study was carried out on 42 individuals (22 with heart disease taking warfarin drug as case group and 20 healthy individuals as control group). Non-stimulated whole saliva samples were obtained by expectoration. Salivary flow rate was measured as ml/min, salivary C-reactive protein and albumin levels were measured by using auto-analyzer. Periodontal status was assessed by measurement of clinical attachment loss for both groups.

The mean salivary flow rate was significantly lower in case group compared to healthy controls ( $P=0.02$ ). The mean salivary C-reactive protein and albumin levels were significantly higher in the case group than the control group ( $p=0.003$ ). Clinical attachment loss was significantly higher in case group than controls ( $p<0.001$ ).

Salivary flow rate decrease in patients with heart disease. Salivary C-reactive protein and albumin levels in addition to clinical attachment loss were increase in patients with heart disease using warfarin drug, so good oral hygiene instructions are necessary.

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### Introduction

The term heart disease refers to several kinds of heart conditions. Coronary artery disease is the most common one, which results in heart attack. The other types of heart diseases include the valves in the heart, or the heart cannot pump well which leads to heart failure. Some individuals are born with heart disease.<sup>1</sup>

The symptoms differ according to the type of the disease, but heart attack or chest discomfort is the first sign for many patients. Many tests like chest X-rays, coronary angiograms,

electrocardiograms in addition to exercise stress tests can be used for the diagnosis.<sup>1</sup>

Warfarin (WAR) is the most common oral anticoagulant medication used in treatment of various conditions like atrial fibrillation (AF), myocardial infarction, pulmonary embolism and postoperative treatment of prosthetic valve surgery.<sup>2</sup> The therapeutic range is narrow (INR from 2 to 3) and it is a subject for interactions with other medications and foods that may increase or decrease its anticoagulation effect.<sup>3</sup> In the liver, the cytochrome (CYP) P450 is responsible for the metabolism of warfarin for inactivation of hydroxylated metabolites.<sup>4</sup>

Bleeding is one of the most common side effects of warfarin.<sup>5</sup> Regarding the oral cavity, patients treated with warfarin suffer from bleeding from the gingiva on teeth brushing and this make them avoid brushing their teeth. For this reason the prevalence of periodontal disease increases in many Warfarin users.<sup>6</sup>

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The bleeding is usually mild but has high incidence, thus, it is believed that gingival bleeding due to using Warfarin worsen the periodontal disease.<sup>7</sup>

Saliva plays a chief role in the oral ecosystem. Its buffering system through bicarbonate ion neutralizes acidity of the oral cavity and prevents dental caries. Salivary anti-bacterial effect is important in maintenance of oral microbial balance.<sup>8</sup>

Periodontitis can be defined as an inflammatory condition affecting the supporting tissues of the teeth and caused by specific microorganisms. It is characterized by extensive destruction of periodontal tissue and alveolar bone with formation of pocket, gingival recession or both. Gingivitis is an inflammatory disease of gum and clinically the presence of attachment loss in periodontitis makes it be distinguishable from gingivitis.<sup>9</sup> C - reactive protein (CRP) is protein synthesized in the liver. Its half-life is approximately 4-6 hours. The serum levels of CRP increase rapidly within 24 to 72 hours in response to inflammation or tissue damage and will decrease after the removal of inflammation or infection.<sup>10</sup>

CRP has a key role in atherosclerosis, if it increases by more than 0.5 milligrams per liter, the risk of cardiovascular diseases increases.<sup>11</sup> A correlation between periodontitis and cardiovascular diseases has been suggested in several studies. It has been found that there are some relations between periodontal disease and atherosclerotic heart disease and heart attacks and strokes. Although the cause and effect relationship has not been established, but it seems that increase CRP levels in periodontitis may help to explain the relationship between cardiovascular diseases and periodontitis.<sup>11</sup>

Several studies have been done to investigate the relationship between salivary CRP levels and periodontal disease. Among these studies Giannobile et al. found that salivary and serum CRP levels were elevated in patients with chronic and aggressive periodontitis.<sup>12</sup>

Albumin (ALB) is the most abundant serum protein, forming more than 50% of all plasma proteins. It is synthesized in the liver exclusively. In the oral cavity, it is regarded as a serum ultra-filtrate to the mouth and it may also diffuse into the mucosal secretions.<sup>13</sup>

Salivary ALB has been shown to be elevated in medically compromised patients with

worsen general condition. Immunosuppression, diabetes and radiotherapy are examples of the conditions in which high levels of salivary albumin have been determined.<sup>14</sup> It may be hypothesized that salivary albumin can be used to determine mucosal function integrity in the mouth.<sup>15</sup>

The purpose of this study was to assess salivary flow rate, C- reactive protein and albumin levels with assessment of periodontal condition in patients with heart disease under warfarin treatment.

## Materials and methods

### Subjects

Forty two individuals were enrolled in this study; the case group includes 22 patient with heart disease taking warfarin (13 male and 9 female with a mean age of  $63.2 \pm 14.8$  years) and the control group includes 20 non warfarin users' subjects without a past history of systemic or cardiovascular problem (11 male and 9 female with a mean age of  $60.12 \pm 7.3$  years). Smokers were excluded from the study. Before starting investigation, consent form was obtained from all subjects participated in the study.

### Collection of saliva

Each subject asked to rinse his mouth then to spit in sterile cup. Saliva was collected from each subject for 10 minutes and the flow rate was measured as ml/min. After collection of saliva, the samples were kept in a refrigerator then centrifuged at 3,000 rpm for 10 min. The clear supernatant was transferred to small tubes and these tubes were stored frozen at  $-80^{\circ}\text{C}$  and thawed before analysis.

### Chemical analysis

C-reactive protein (CRP) and albumin (ALB) were analyzed by using auto-analyzer (HITACHI, Japan) using immuno-turbidity method.

### Oral cavity examination

For evaluation of periodontal condition, gingival recession was evaluated by measuring the distance from free gingival margin to the cement- enamel junction (CEJ). Pocket depth (PD) was assessed by measuring the coronal-apical extension or the depths of the periodontal pocket.<sup>16</sup> For measuring of clinical attachment loss (CAL), the level of the gingival margin

(distance from CEJ to gingival margin) was subtracted from the probing pocket depth.<sup>17</sup>

#### Statistical analysis

Mean and standard deviation were used to illustrate the difference in age between case and control groups. Student's unpaired t-test was used for comparison of salivary flow rate, CRP, ALB levels and the clinical attachment loss between the two groups. P value less than 0.05 was considered statistically significant.

### Results

No significant difference was found between case and control groups regarding the age and sex ( $p=0.08$  and  $p=0.07$  respectively).

Regarding the salivary flow rate, a significant difference was noticed between the two study groups. The mean salivary flow rate was significantly lower in patients with heart disease treated with warfarin in comparison to healthy individuals ( $p=0.02$ ) (table 1).

The mean salivary ALB and CRP levels were significantly higher in case group than control group ( $p=0.003$ ) (table 1).

A high significant difference was noticed between the two groups regarding the clinical attachment loss (CAL). The mean clinical attachment loss level was significantly higher in case group than control group ( $p<0.001$ ) (table 2).

### Discussion

The function of the platelet and blood coagulation ability are increase after prosthetic valve surgery, for this reason the use of anti-platelet drugs are important for those patients.<sup>18</sup> It was found that warfarin drug is more preferable than the prolonged use of aspirin drug as preventive measure for cardiac complications.<sup>19</sup>

Saliva is a complex body fluid, it is important for oral health and several studies have been done using saliva as a diagnostic element for many systemic diseases and for drugs monitoring purposes.<sup>20, 21, 22</sup>

In the present study, salivary flow rate, ALB and C-reactive protein in addition to clinical attachment loss level in individuals with heart disease using warfarin drug were determined and compared to healthy controls.

The mean salivary flow rate was significantly lower in patients with heart disease than healthy individuals ( $p=0.02$ ). This result is in accordance with the result of Hegde et al., they found that salivary pH and flow rate were significantly decreased in cardiac patients and there was association with the level of salivary sialic acid; they were suggested that sialic acid could be used as a good predictor for the severity of oral disease in those patients.<sup>23</sup>

In another study by Hamed et al. salivary flow rate, secretory IgA, pH and phosphorus were significantly decreased in children with congenital heart disease in addition to worse dental status as compared to control group.<sup>24</sup>

The decreased salivary flow rate in heart disease patients could be attributed to the side effects of drugs including the anticholinergic activity of drugs such as cardiovascular agents, like furosemide, digoxin and enalapril were commonly taken by the patients.<sup>25</sup>

Salivary ALB level showed high level in case group compared to control group, this result is in agreement with that of Mellanen and also consistent with that of Azizi A., et al., they reported increase salivary ALB levels in patients treated with warfarin.<sup>26, 27</sup>

The high level of salivary ALB may be caused by transudation of the components of serum into the mouth and is considered as an ultra-filtrate of serum to the oral cavity, also it may diffuses into the mucosal secretions.<sup>28</sup>

The mean salivary C-reactive protein level was significantly high in heart disease patients treated with warfarin compared to controls, this result agree with the findings of Christodoulides et al., they found that C reactive protein level increase in cardiovascular disease and regarded it as a good indicator of the disease.<sup>29</sup>

The same result was seen by Saiko et al., they noticed that salivary components including ALB and CRP were increase in patients using warfarin treatment and there was a correlation between these components and periodontal parameters including gingival index, plaque index and clinical attachment loss.<sup>30</sup>

Clinically, C-reactive protein levels in the circulation have been used as a marker and as a predictor of general inflammation and risk status of cardiovascular disease.<sup>31</sup> The levels of CRP in oral fluids are highly correlated with levels in the circulation.<sup>32</sup> C-reactive protein secreted primarily

by the liver and circulatory levels increase in response to systemic and local inflammation.<sup>33</sup>

It is found that chronic inflammation results in mild increase in circulatory CRP level and increased risk for cardiovascular diseases due to its involvement in atherosclerosis<sup>34</sup>, whereas high levels of CRP in circulation refers to acute inflammation or infections.<sup>35</sup>

The molecule of CRP is too large which make its passage from the blood to the saliva by diffusion is difficult; it is proposed to enter saliva secretion as a constituent of gingival crevicular fluid.<sup>32</sup>

Clinical attachment loss level was significantly high in case group than control group; this result is in agreement with that of Saiko et. al, they found a significant difference between plaque index, gingival index and clinical attachment loss level in case and control groups.<sup>30</sup>

The result is also in accordance with the result of Azizi A., et al, they reported that periodontal clinical parameters in patients taking warfarin were higher than healthy subjects and a significant correlation was shown in, GI, CAL and salivary albumin.<sup>27</sup>

Several investigations including epidemiological, clinical and animal studies suggest a relationship between periodontal diseases and heart diseases and basic laboratory investigations point to the possibility of biological association due to the presence of oral bacteria in carotid atheroma.<sup>36</sup>

## Conclusions

It seems that salivary flow rate decreases in Patients with heart disease taking warfarin treatment. Salivary albumin and C - reactive protein levels increase in those patients. The periodontal condition worsens in patients with heart disease on warfarin treatment so good oral hygiene instructions for those patients are required.

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