Correlation between Salivary and Serum CRP Levels in Urticaria Patients

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Abstract: Urticaria are commonand has a detrimental effect on that adversely impacts the quality of life. Urticaria occurs due to mast cell activation and subsequently followed by inflammatory response. C- reactive protein (CRP), the prototypical acute-phase reactant has been used widely on-specific clinical indicator to assess systemic inflammatory status. Development of salivary CRP assays that is non-invasive, stress- and pain-free may constitute an alternative strategy. To the best knowledge of author, there have been no studies done on the correlation of saliva and serum CRP in urticaria patients. The objective of this study was to find the correlation between salivary and serum CRP levels in patients with urticaria. The study design was cross-sectional observational analytic and 21 urticaria patients were recruited. Saliva and serum CRP levels were measured within 48 hours of lesion onset using immunoturbidimetry and ELISA method. Statistical analysis of the Pearson correlation coefficient was used Saliva CRP concentrations ranged from $3{,}00x10^{-6}$ mg/L to $1{,}77x10^{-3}$ mg/l, mean values were $3{,}77x10^{-4}$ mg/l ($\pm$ $4{,}72x10^{-4}$). Serum CRP concentration ranged from 0,40 mg/lto17,40 mg/l, mean values 3,28 mg/l (±3,85). We found a verystrongassociation CRP measured in saliva with serum CRP($r = .814$, $p < .05$). Salivary CRP measurement may thus facilitate alternative method of CRP serum to know inflammatory state in patients with urticaria.

1 INTRODUCTION

Urticariais a distressing disorder that adversely impacts the quality of life; yet it spathogenesis is not well delineated and, accordingly, thetreatment is often palliative and therapeutic outcome is suboptimal (Jain., 2014). Mast cell activation accompanied by inflammatory response is associated with urticaria, which may be manifested by increased serum concentration of C- reactive protein (CRP) (Kasperska et al, 2011). It has been demonstrated that circulating CRP concentration is increased in acute and chronic urticaria, and furthermore CRP concentrations correlate with the disease severity. Therefore, characterization of CRP in urticaria may be essential to gain better insight into the activity of the disease and to assess the degree of inflammation (Kasperska, 2012).

The presence of CRP molecules in saliva and recent technical advances provides an opportunity for development of non-invasive assessments of disease which would enable research in large population representative samples and in young people (Oullet, 2011). However, salivary CRP reference ranges and their correlation with serum levels are not established. In addition, although a correlation between serum and salivary CRP concentration has been observed this relationship has not been investigated in urticaria subjects. The goal of the study reported here was to investigate the relationship between salivary and blood serum levels of this molecules in patients with urticaria.

2 METHODS

2.1 Subjects and Sample Collection

Study participants were21urticaria patients (76.2% women) aged between 19 and 55 years (mean (SD) = 34.7 (11.8)). None reported comorbid disease (cardiovascular, Diabetes mellitus, autoimmune or liver), vasculitis or pressure urticaria, pregnancy and overweight. Moreover, no participant reported on corticosteroid or systemic immunomodulator.

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Participants were recruited from Dermatovenereology outpatient department of Saiful Anwar General Hospital. Participants gave informed consent. The study protocol was approved by Saiful Anwar General Hospital Research Ethics Commmitte. The subjects were asked to fast for at least 30 minutes prior to giving their blood and saliva samples. Unstimulated whole saliva was obtained using the passive drool method (approximately 5 ml) and the saliva samples were immediately placed on ice following collection and stored at -20 °C. Blood samples were collected by venipuncture into vacutainer tubes and were immediately centrifuged to separate blood components and measured.

2.2 C-reactive Protein Measurement

The concentration of CRP in saliva was determined using ELISA method. C-reactive protein (CRP) levels in serum were determined using turbidimetry method using semiautomated analyzer.

2.3 Statistical Analyses

The association between salivary with serum CRP was investigated using parametric (Pearson r) and nonparametric (Spearman r). Difference in variations in salivary and serum CRP mean levels of various variables were analyzed with One-way Anova and T-test.

3 RESULTS

3.1 Descriptive Data

In the study, total numbers of patients were 21 urticaria patients. Salivary CRP concentrations ranged from 3.0 pg/ml to 1769.67 pg/ml (mean (SD) = 377.44 (471.7)). From the total sample (n = 21), none of these participants had salivary CRP values that exceeded from the mean reported in healthy adults (6131.40 pg/ml) (Salimetrics, 2011). Higher values were observed for serum CRP (range = .4–17.48 mg/dl; mean (SD) = 3.28 (3.85)).) The CRP levels differed little from some variables (Table 1). The levels of CRP serum were higher in women. Both salivary and serum CRP levels were significantly higher in the presence of lesion in time of measurement.

Table 1: Salivary and Serum CRP levels between Variables.

Subjects Characteristic	SalivaryCRP mean (mg/l) ± SD	*p-value**	Serum CRP mean (mg/l) ± SD	*p-value**
Age (years)				
18 - 30	$1{,}77x10^{-4} \pm 1{,}67x10^{-4}$	0,216	2,26 ± 1,93	0,323
31 - 45	$4{,}76x10^{-4} \pm 5{,}83x10^{-4}$		3,18 ± 2,71	
46 - 55	$6{,}31x10^{-4} \pm 6{,}20x10^{-4}$		5,80 ± 7,74	
Sex				
Men	$7{,}10x10^{-4} \pm 5{,}00x10^{-4}$	0,070	7,28 ± 6,11	**0,004***
Women	$2{,}74x10^{-4} \pm 4{,}26x10^{-4}$		2,03 ± 1,66	
Family History				
Yes	$3{,}60x10^{-4} \pm 4{,}90x10^{-4}$	0,866	2,44 ± 1,79	0,303
No	$3{,}96x10^{-4} \pm 4{,}77x10^{-4}$		4,21 ± 5,24	
Antihistamin use				
Yes	$4{,}88x10^{-4} \pm 5{,}92x10^{-4}$	0,226	3,90 ± 4,83	0,408
No	$2{,}31x10^{-4} \pm 1{,}76x10^{-4}$		2,46 ± 1,87	
BMI				
Underweight	$2{,}40x10^{-4} \pm 3{,}20x10^{-4}$	0,675	1,05 ± 0,21	0,402
Normoweight	$3{,}92x10^{-4} \pm 4{,}89x10^{-4}$		3,52 ± 3,98	
Lesion				
Presence	$6{,}94x10^{-4} \pm 7{,}63x10^{-4}$	**0,049***	5,92 ± 6,23	**0,044***
Absence	$2{,}51x10^{-4} \pm 2{,}23x10^{-4}$		2,23 ± 1,76	

Onset Last Lesion				
<19 hours	$3,32x10^{-4} \pm 4,23x10^{-4}$	0,290	2,66 ± 2,24	0,066
>19 hours	$6,51x10^{-4} \pm 7,58x10^{-4}$		7,03 ± 8,98	
Angioedema				
Yes	$3,54x10^{-4} \pm 5,61x10^{-4}$	0,850	2,58 ± 2,14	0,482
No	$3,95x10^{-4} \pm 4,18x10^{-4}$		3,81 ± 4,78	
Urticaria Type				
Acute	$3,50x10^{-4} \pm 4,42x10^{-4}$	0,768	3,81 ± 4,85	0,482
Chronic	$4,14x10^{-4} \pm 5,33x10^{-4}$		2,58 ± 1,91	

*Bold text indicates a statistically significant difference with a p-value less than 0.05

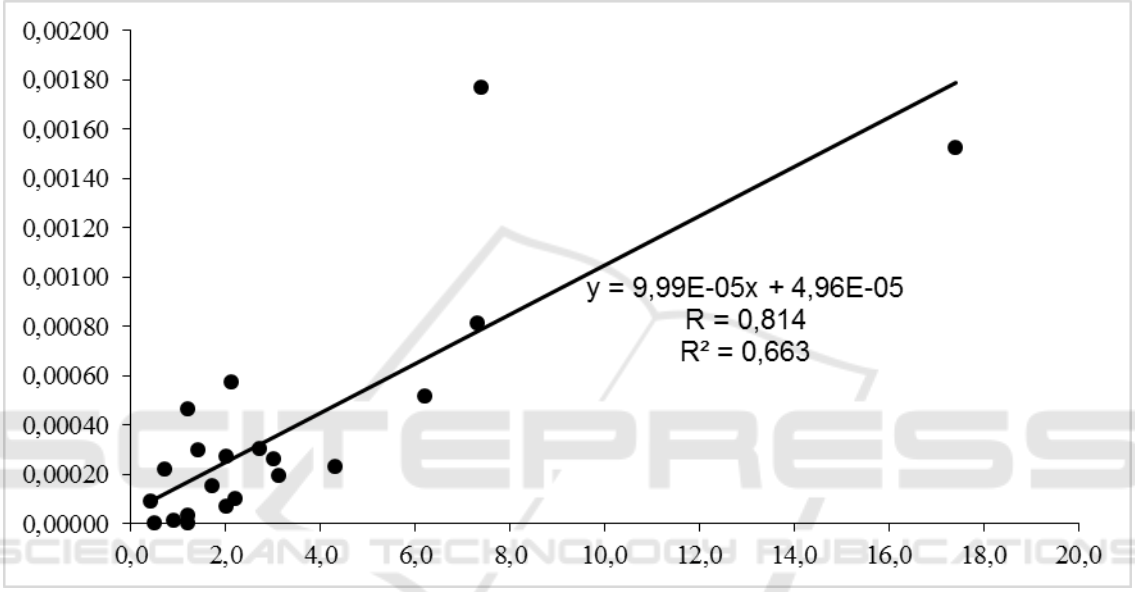

Figure 1: Correlation between salivary CRP and serum CRP in urticariapatients.x = serum CRP, y= salivary CRP, R= Correlation Coefficient, R^2 = Coefficient of Determination.

3.2 Associations between Salivary with Serum CRP Levels

As shown in **Fig. 1**, the correlation between salivary and serum CRP was r = .81 (very strong). The saliva-to-serum ratio was low (1:8700). The following equation can be used to predict serum CRP from saliva: y = 999.04x + 49.66 where y = salivary CRP and x = serum CRP.

4 DISCUSSION

We observed a very strong association between CRP measured in saliva and serum. Our study provides supporting evidence suggesting that non-invasive assessment of CRP in saliva allows the valid prediction of serum CRP. Consistent with that result, strong saliva and serum CRP correlations were reported in animal studies, such as in healthy (r = .87) and diseased dogs (r = .84) and in pigs (r = .73) (Parra et al, 2005; Gutiérrez et al, 2009). Our study was also consistent with previous validation study that found moderate to strong association in healthy subjects. Our finding was however inconsistent with the absence of association found between serum and salivary CRP in medical students (Dillon et al, 2010).

The salivary CRP measure could be improved in future studies by exploring three issues in this study. First, there was significant difference in serum CRP levels between men and women, probably due to one men participant had a great extent of serum CRP values than mean level (530%) with unclear explanation. There was also significant difference in salivary and serum CRP according to the presence of

lesion in time of measurement. Our finding suggests that salivary CRP determination requires all the patients show active urticaria at the time of assessment.

Second, given the low saliva-to-serum CRP ratio, it is possible that high-sensitivity ELISA may not be sensitive enough to precisely quantify CRP in saliva, particularly at low concentrations. Other analytical methods have been used to determine CRP from saliva, including time-resolved immunofluorometric assays surface plasmon resonance immunosensor, magnetic immunosensor, and lab-on-a-chip devices. While these analytic strategies may be most remain under development and thus are not readily accessible to researchers, it should be explored further whether the collection of larger saliva volume or parotid saliva may optimize the measurement of CRP in the saliva.[4] Third, replication in larger samples is needed due to large Standard of Deviation (SD) in the result of our study.

This study provides supporting evidence for the validation of salivary CRP as an alternative marker for inflammation using a broadly available technology adapted to saliva specimens. Saliva sampling is non-invasive, stress-free, can be easily performed in the participants' natural settings and can be repeated over time. Moreover, saliva collection has considerable economical and logistic advantages over venipuncture because it does not require immediate manipulations, access to specialized laboratory equipment's and qualified personnel (Oullet et al, 2011). Furthermore, future studies should extent the present findings and correlate measurement of salivary CRP with urticaria clinical severity as well as therapy evaluation.

5 CONCLUSIONS

This study demonstrates a very strong positive correlation between salivary and serum CRP in urticaria patients.

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