Reflections of the Anti-inflammatory Properties of Aspirin on Cardiovascular Disease and Diabetes Mellitus-related Pathological Markers

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ABSTRACT
To keep track of immune modulating effects of using prophylactic acetylsalicylic acid (ASA) or aspirin in Iraqi community, 60 selected patients taking aspirin were divided into two groups, depending on their medical conditions, group I (30 patient having cardiovascular disease), group II (30 patient having diabetes mellitus), versus 20 matched corresponding patients, don’t take aspirin, who were depended as control groups (ten each). All were tested for their inflammatory markers including levels of interleukin-1β (IL-1β), interleukin 6 (IL6) and high sensitivity C-reactive protein (hsCRP) by using ELIZA technique. Results recorded decreased levels of IL1β (0.357±0.03pg/ml) and IL6 (2.22±0.26pg/ml) in group I and (0.250 ± 0.02pg/ml) (1.450 ± 0.22pg/ml) in group II, compared to their counterparts (5.31±1.29pg/ml) (12.66±1.46pg/ml), and (5.58±1.29pg/ml) (7.63±0.75pg/ml) in succession. Such results indicate the beneficial immune regulatory action of aspirin in cardiovascular and diabetic patients. Rather hsCRP showed no significant variations in both groups of patients compared to their controls; (4.039±0.29ng/ml vs 3.290±0.65ng/ml) and (5.06 ± 0.40ng/ml vs 6.29±0.54 ng/ml), respectively.

INTRODUCTION
Acetylsalicylic acid (ASA) or aspirin, which is the most common non-steroidal anti-inflammatory drug (NSAID), has been approved by the Food and Drug Administration (FDA) to prevent heart attacks and strokes in people at high risk of developing them. Aspirin affects components of the innate and adaptive immune system and can stimulate their proliferation, maturation, and cytokine synthesis [1]. Aspirin reduces the inflammatory response that is a major component in cardiovascular disease (CVD) and diabetes [2], Interleukin IL1β, IL6 and hsCRP, are inflammatory markers serve in grading of metabolic syndrome predisposing to cardiovascular disease [3]. These mediators are released as a response to injured endothelium by various risk factors like hypertension, and promote the interaction of endothelium with circulatory leukocytes, as in diabetes mellitus related to failure of β-cell function and reduction of β-cell mass [4–9].

SUBJECTS AND METHODS
Sixty patients were divided into two groups depending on medical condition. Group I included 30 patients with CVD and group II included 30 patients with type 2 diabetes mellitus. Both groups were taking aspirin regularly (100mg) once daily for more than six months. The diagnosis in each case was established by clinical examination and recommended investigation. The age range of group I was from (35 to 65 years) with a mean of (53.56 ± 1.08 years). Ten patients with CVD were not taking aspirin, with age range from (35 to 65 years) with a mean of (51.10 ± 2.74 years) were enrolled in the study as control group for group I patients. Whereas group II of diabetic patients were with age range from (35 to 65 years) with a mean of (53.20 ± 1.25years), to whom a matched ten diabetic patients, but don’t taking aspirin with a mean age of (50.00 ± 2.70 years) were depended as a control group. To investigate the effect of prophylactic aspirin on healthy subjects, ten apparently healthy volunteers were chosen randomly and investigated for their levels of IL1β, IL6, and hsCRP in two occasions; the day before start taking aspirin and after 30 days of taking aspirin (100mg) once daily. The criteria of exclusion comprise other chronic diseases, established anti-inflammatory therapy other than aspirin, including (NSAID, cortisone), receiving immunosuppressive treatment or vitamins and cases had history of allergy to aspirin.

RESULTS AND DISCUSSION
Cardiovascular disease patients in group I revealed reduced inflammatory cytokines as shown in (table 1). The inflammatory markers represented by IL1β was recorded a mean of (0.357 ± 0.03pg/ml) in group I as compared to its control group who were not taking aspirin, whose mean value was (5.31 ± 1.29pg/ml) with a highly significant difference (P<0.0001). Likewise, Aspirin in the group II (diabetics who were taking aspirin) lowered the IL1β level, which made it with a mean of (0.250 ± 0.02pg/ ml) compared to diabetic patients who did not take aspirin and whose mean was (5.58 ± 1.29pg/ml). Interleukin-6 in group I reduced to a mean of (2.22 ± 0.26pg/ml) compared to the control group whose mean was (12.66 ± 1.46pg/ml). Statistically, there was a highly significant difference between the two groups (P<0.0001). There was a similar effect to aspirin in the group of diabetics, where it recorded a mean (1.450 ± 0.22pg/ ml) compared to that recorded in the control group, whose mean value was (7.63 ± 0.75pg/ ml). Statistically, there

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was a highly significant difference between such groups (P< 0.0001).
Here, the role of aspirin is clear in mitigating the noxious effects of these inflammatory mediators and their roles in pathological events, whether in patients with diabetes or CVD. In this regard, there are studies that have recorded effects of aspirin in reducing levels of IL6 \cite{6}, and others have recorded effects even in improving insulin resistance \cite{7}.

Highly sensitive CRP levels in group I and group II revealed no significant affectability from Aspirin. The mean levels of the two groups were equal to (4.039 ± 0.29ng/ml and 5.06 ± 0.40ng/ml) respectively compared to their controls, which had means of (3.290 ± 0.65 ng/ml and 6.29 ± 0.54ng/ml) consecutively. The above results are summarized in the (table 1).

Table 1. Inflammatory markers in CVD and Diabetics compared to control groups

<table>
<thead>
<tr>
<th>Inflammatory marker</th>
<th>Group I (n=30)</th>
<th>Control (n=10)</th>
<th>Total (n=40) P value</th>
<th>Group II (n=30)</th>
<th>Control (n=10)</th>
<th>Total (n=40) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL1β pg/ml</td>
<td>0.357±0.03</td>
<td>5.31±1.29</td>
<td>0.0001 H.S</td>
<td>0.250±0.02</td>
<td>5.58±1.29</td>
<td>0.0001 H.S</td>
</tr>
<tr>
<td>IL6 pg/ml</td>
<td>2.22±0.26</td>
<td>12.66±1.46</td>
<td>0.0001 H.S</td>
<td>1.450±0.22</td>
<td>7.63±0.75</td>
<td>0.0001 H.S</td>
</tr>
<tr>
<td>hsCRP ng/ml</td>
<td>4.039±0.29</td>
<td>3.290±0.65</td>
<td>0.247 N.S</td>
<td>5.06±0.40</td>
<td>6.29±0.54</td>
<td>0.1157 N.S</td>
</tr>
</tbody>
</table>

Regarding the results of healthy volunteers who were used prophylactic Aspirin, after one month of using it they recorded a slight reduction in the levels of the three inflammatory parameters IL1β, IL6, and hsCRP compared to their baselines levels.
The recorded means were as follow (1.637±0.46pg/ml vs 2.427±0.58pg/ml) for IL1β, (5.531±0.83pg/ml vs 6.216 ±0.89pg/ml) for IL6, and a mean of (4.163±0.31ng/ml vs 5.872±0.20ng/ml) for hsCRP respectively, and as shown in (table 2).

Table 2: Inflammatory markers in healthy volunteers who were used prophylactic Aspirin compared to control group

<table>
<thead>
<tr>
<th>Inflammatory marker</th>
<th>before (n=10)</th>
<th>after (n=10)</th>
<th>Total (n=10) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL1β pg/ml</td>
<td>2.427 ± 0.58</td>
<td>1.637 ± 0.46</td>
<td>0.307 N.S</td>
</tr>
<tr>
<td>IL6 pg/ml</td>
<td>6.216 ± 0.89</td>
<td>5.531 ± 0.83</td>
<td>0.582 N.S</td>
</tr>
<tr>
<td>hsCRP ng/ml</td>
<td>5.872 ± 0.20</td>
<td>4.163 ± 0.31</td>
<td>0.439 N.S</td>
</tr>
</tbody>
</table>

This unclear impact of Aspirin on such an inflammatory element could be attributed in part to the low dose of this medication and for the short duration of use compared to the above totals. However, the slight effect of aspirin cannot be completely ruled out.
The effect of aspirin on hsCRP is still controversial and some other studies concluded that aspirin works on reduction of the hsCRP level to a certain limit only, but not enough to make significant importance \cite{8}.
With the association of diabetes and CVD to the various predisposing and risk factors \cite{9}, however, inflammatory mediators have a share in their emergence and exacerbation \cite{10,11,12,13}. Therefore, scientific efforts are continuing to search for what curb such harmful effects.

CONCLUSION
IL1β and IL 6 represent overt targets for Aspirin; their reduced levels, and what follows of immunomodulatory events, pour in the favor of achieving the goals of treatment.

REFERENCES


