Platelet Histogram Indices and Cardiovascular Disease in Patients with Rheumatoid Arthritis

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Background. Previous studies reported the increased prevalence of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) compared to the general population. However, the predictors for the development of CVD in patients with RA were not clearly established, and the role of thrombosis mechanisms was inconsistently characterized in these patients. The aim of this study was to evaluate the platelet histogram indices, as markers of platelet activation, in patients with RA with or without CVD.

Material and methods. In 64 pts with RA (mean age: 58.0±12.7 yrs) we performed the standard clinical evaluation and biochemical workup with platelet histogram, including mean platelet volume (MPV) and platelet distribution width (PDW) as markers of platelet activation. We divided the study population into two groups: A – 41 patients with RA without CVD and B – 23 patients with RA and CVD (ischemic heart disease, peripheral artery disease or cerebrovascular disease). The values of MPV and PDW were also analyzed in an age- and sex-matched control group of 20 subjects without RA and CVD and in a group of 62 patients with CVD without RA (stable angina).

Results. The platelets number was similar in both groups, but the platelet histogram showed higher values for MPV (9.6 vs 8.6 fL, p<0.01) and PDW (16.1 vs. 14.0, p<0.01) in patients with RA and CVD, reflecting greater platelet activation in these patients. MPV values were lower in patients with RA, but the values of PDW were higher in these patients comparing to control. Patients with RA with CVD have higher values of PDW than patients with CVD, but without RA, showing an increased platelet activation in RA. The PDW values correlate with fibrinogen (0.63; p=0.003) but not with CRP or ESR, while the MPV was not correlated with the inflammatory markers in patients with RA.

Conclusions. The pathogenesis of CVD in patients with RA may be linked to an increased prothrombotic activity which might be evaluated by platelet histogram indices.

Key words: rheumatoid arthritis, cardiovascular disease, mean platelet volume, platelet distribution width.

Previous large epidemiological studies showed the large prevalence of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA). In the study of Wallberg-Jonsson et al. the mortality ratios for cardiovascular disease (OR 1.46) and for ischemic heart disease (OR 1.54) were higher in RA compared to control population [1]. In patients with RA there is an increased risk for myocardial infarction which was linked with the parental history of myocardial infarction before 60 years [2] or with the hyperlipidemia [3]. Other studies reported an increased prevalence for stable angina [4] in RA patients. Not only the prevalence of cardiovascular disease was increased in RA, but also subclinical vascular changes were described [5]. Increased values for intima-media thickness, as marker of subclinical atherosclerosis, were reported in patients with RA [6]. Endothelial dysfunction and an increased vascular stiffness were equally described in patients with RA [7]. The multivariate analysis showed that this increased risk was not related to traditional cardiovascular risk factors, but merely seems to be related to persistent inflammatory status in these patients, the proposed mechanisms including several pathways and mediators (C-reactive protein, TNF-alpha, IL-6, osteoprotegerin, adhesion molecules, “proinflammatory” HDL-cholesterol, homocysteine etc.) [8].

Several studies reported that platelet histogram indices – mean platelet volume (MPV) and platelet distribution width (PDW) – might be considered as platelet activation markers [9], as during the activation process the platelets became larger. PDW, also routinely reported by modern analyzers together with MPV, might be regarded as a marker of platelets activation, in fact reflecting a more important heterogeneity of the platelets dimensions. In clinical studies, this very simple to obtain indices were linked to cardiovascular disease (acute coronary syndromes [10], myocardial infarction [11], stroke [12]) and with the presence of cardiovascular risk factors [13] in general population.

Thus, the aim of our study was to evaluate these platelet indices in patients with RA with or without cardiovascular disease.

MATERIAL AND METHODS

We included 64 patients with RA, diagnosed with RA according to American College of Rheumatology criteria. A standard file was completed for each subject, and consisted of the demographic characteristics, clinical and laboratory parameters. Individual and family history of cardiovascular disease or diabetes and the presence of other traditional cardiovascular risk factors including smoking status, hypertension, and high cholesterol levels were also included in this file. We also noted the presence of known cardio-vascular disease (ischemic heart disease, peripheral artery disease or cerebrovascular disease). Ischemic heart disease was defined as a known history of myocardial infarction, unstable or stable angina, or history of coronary revascularisation procedures. Peripheral artery disease was defined as history of claudication or revascularisation procedures, and cerebrovascular disease as a history of transient ischemic attack, stroke or revascularisation procedures. We performed the standard measurements of weight, height, systolic and diastolic blood pressure, standard biochemical workup, including the levels of fibrinogen, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as inflammatory markers and also the platelet histogram from which we analyzed mean platelet volume (MPV) and platelet distribution width (PDW) as markers of platelet activation. Blood samples for hemolucogram were collected in the supine position from the antecubital vein using an ethylene-diaminetetraacetic acid (EDTA) containing tube and were analyzed within 2 hours from venipuncture using the automated analyzer.

We divided the study population into two groups: A – 41 patients with RA without CVD and B – 23 patients with RA and CVD. The values of MPV and PDW were also analyzed in an age- and sex-matched control group of 20 healthy subjects without RA or CVD and in a group of 62 patients with CVD (stable angina) but without RA. The diagnostic of patients with stable angina was performed according to current guidelines.

The exclusion criteria from the study were: active cancers (solid cancers or hematological cancers); acute (at the moment of inclusion or in the last three months) or chronic infections; granulomatous chronic diseases (sarcoidosis); age < 18 years; pregnancy or post-partum period (six months); severe chronic renal failure.

Statistical analysis was performed using JMP IN 5.1.2. (SAS® Institute). All reported p values were considered significant at a level of P<0.05.

RESULTS

The mean age was similar in the four groups of patients included in our study (Table I). The platelets number was similar in both groups, but the platelet histogram showed higher values for MPV (9.6 vs. 8.6 fL, p<0.01) and PDW (16.1 vs. 14.0, p<0.01) in patients with RA and CVD vs those with no CVD, reflecting greater platelet activation in these patients (Figs. 1 and 2).

<p>| Table I |
| Baseline characteristics of the patients groups |</p>
<table>
<thead>
<tr>
<th>Controls (no RA, no CVD)</th>
<th>RA without CVD</th>
<th>RA with CVD</th>
<th>CVD (stable angina), no RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>20</td>
<td>41</td>
<td>23</td>
</tr>
<tr>
<td>Mean age (yrs)</td>
<td>61.6 ± 11.2</td>
<td>56.1 ± 13.6</td>
<td>60.1 ± 12.0</td>
</tr>
<tr>
<td>Platelet number (mm$^{-3}$)</td>
<td>242348.6±98767.4</td>
<td>312888.3±114397.5</td>
<td>303333.4±108362.1</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>9.6 ± 0.3</td>
<td>8.6 ± 0.2</td>
<td>9.6 ± 0.4</td>
</tr>
<tr>
<td>PDW</td>
<td>11.8 ± 1.2</td>
<td>14.0 ± 0.8</td>
<td>16.1 ± 1.2</td>
</tr>
</tbody>
</table>
MPV values were lower in patients with RA (8.6 vs 9.6, p<0.05), but the values of PDW were higher in these patients compared to control (14.0 vs. 11.8, p<0.01).

Patients with RA and CVD have higher values of PDW than patients with CVD, but without RA (16.1 vs. 13.4, p<0.05), showing an increased platelet activation only linked to the presence of RA.

The PDW values correlate significantly with fibrinogen values (r=0.63; p=0.003) but not with CRP or ESR, while the MPV was not correlated with the inflammatory markers.

**DISCUSSION**

This is one of the first studies showing that platelet activation markers are increased in patients with RA and CVD as compared both with patients with RA without CV complaints, but also to general patients with CVD, reflecting a higher prothrombotic activity in this population.

The prothrombotic factors were previously found to be associated with an increased cardiovascular risk and with cardiovascular events in general population and also in patients with RA. McEntegart *et al.* reported higher levels of prothrombotic factors (fibrinogen, von Willebrand factor, tissue plasminogen activator antigen (t-PA) and D-dimers) in patients with RA than in controls [4]. It is well known that platelets number is increased in patients with RA and also a link was reported between thrombocytosis and severe disease or extraarticular manifestations of the disease [14,15].

Platelets histogram indices, like MPV (mean platelet volume) and PDW (platelet distribution width), are usual indices reported by hospital laboratories in daily clinical practice. Several previous reports showed the utility of MPV and PDV as markers of platelet activation [16] based mainly on the fact that in this activation process the platelets change the shape and the volume. Otherwise, MPV and PDW, as markers of platelets activation, were demonstrated to have prognostic importance in patients with cardiovascular disease and a large volume of may be regarded as a marker of platelets activation.

In our study group, patients with RA without CVD have lower values of MPV and higher values of PDW than controls. There are some conflicting data in the literature concerning the values of MPV in patients with RA. Kisacik *et al.* reported lower values of MPV in patients with active RA than controls (patients with osteoarthritis) and these values significantly increased after treatment, but remained lower than in control patients [17]. Yazici *et al.* reported higher values of MPV in patients with RA, which were correlated with the DAS28 disease activity score, decreasing after the treatment [18]. Otherwise, previous studies reported the fact that the MPV is highly dependent on the time of storage until the analysis [19]. Further large and standardized studies are required in order to obtain valid conclusions concerning the MPV values in patients with RA.

Also, in our group patients with RA and CVD had higher values of PDW than patients with CVD alone, suggesting a supplementary effect on platelet activation in patients with RA. However, we did not find any difference regarding MPV in these subgroups. There are other authors who also suggest that PDW might be more specific as
platelet activation index than MPV [9]. The link between platelet activation and inflammation was already proven in the literature [20]. As RA is a highly inflammatory status, and atherosclerosis was postulated to have a central inflammatory component, higher platelet activation in these patients might be linked to a higher athero-thrombotic risk. However, the existence of a causal link and the assessment of the magnitude of this relationship in patients with RA both need supplementary prospective studies.

CONCLUSION

The presence of cardiovascular disease in patients with rheumatoid arthritis may be linked to an increased thrombosis activity (fibrinogen levels and platelet histogram indices. Probably, their place as predictors of cardiovascular risk in patients with RA must be regarded as a part of multimarker strategy.

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