Effects of low or medium-dose of prednisone on insulin resistance in patients with systemic lupus erythematosus


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Abstract

Objective
To determine the effect of low (≤7.5 mg/day; LD-PRD group) or medium (>7.5 mg/day; MD-PRD group) doses of prednisone over the past 4 months on insulin levels and insulin resistance (IR) in SLE patients.

Methods
SLE patients were categorised in prednisone non-users (No PRD) (n=41), LD-PRD (n=71) and MD-PRD (n=16) users. We compared insulin levels, presence of increased IR using homeostasis model assessment (HOMA index), metabolic syndrome (MetS), and other clinical, metabolic and inflammatory parameters in the 3 groups. A Spearman’s rho test was used to identify independent associations between daily prednisone dose, HOMA index and insulin levels and other parameters, after adjusting for confounders.

Results
No differences in increased IR, HOMA index and insulin between No PRD and LD-PRD were found. In contrast, the MD-PRD group was younger (p=0.001) and had higher insulin (p=0.013), higher HOMA index (p=0.019) and increased IR (OR 5.8, 95% CI 1.7-20, p=0.007) in comparison with the LD-PRD group. The HOMA index strongly correlated with body mass index (BMI) (r=0.460, p<0.001) but not with clinical activity or inflammatory state after adjusting for confounders. Prednisone dose correlated with the HOMA index and insulin but not with inflammatory parameters (erythrocyte sedimentation rate p=0.075) after adjusting for confounders.

Conclusion
Daily medium-dose prednisone use (>7.5 mg/d) but not low-dose (≤7.5 mg/d) use increased insulin levels and IR in SLE, which may contribute to increased CV risk experienced by these patients.

Key words
Systemic lupus erythematosus, prednisone, corticosteroids, metabolic syndrome, insulin resistance, insulin, atherosclerosis
Prednisone use and insulin resistance in SLE / J.M. Sabio et al.

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Received on December 5, 2009; accepted in revised form on February 1, 2010.© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2010.

Competing interests: none declared.

Introduction
Patients with systemic lupus erythematosus (SLE) have an increased risk of atherosclerotic cardiovascular diseases (ASCVD) morbidity and mortality but the pathogenetic factors involved are not yet fully understood (1). The prevalence of metabolic syndrome (MetS), defined by the presence of central obesity, glucose intolerance, hypertension (HTN), dyslipidaemia and insulin resistance (IR) (2) has been found to be higher in SLE patients, (3-6) especially in those below the age of 40 years old (6). Moreover, a significant association between MetS and subclinical atherosclerosis burden in SLE patients has recently been recorded (7). IR, estimated by homeostasis model assessment (HOMA), predicts incident symptomatic ASCVD in Caucasian subjects among the general population (8), and therefore, it is important to know the factors which contribute to its development. No association has been found between the HOMA index and corticosteroids (CS) use in SLE patients (3, 4). In contrast, Posadas et al. found a positive association between prednisone dosage and insulin levels in paediatric patients with SLE (9). Therefore, no conclusive data are available regarding this issue.

On the one hand, CS may exert a bimodal action on atherogenesis in SLE patients. Firstly, as a result of their anti-inflammatory properties, they may help to decrease atherosclerosis, which is considered an inflammatory vascular disease. In this way, lower prednisone use has been associated with a higher prevalence of carotid plaque in SLE patients (10). On the other hand, CS may have a pro-atherogenic effect because of their well-known adverse effects, including obesity, HTN and dyslipidaemia (11, 12). Moreover, CS are known to induce glucose intolerance, hyperinsulinaemia and IR (13), which have been found to be more prevalent in SLE patients than in sex, age-matched healthy subjects (3, 4, 9). Therefore, it could be of interest to identify a cut-off dosage for corticosteroids in order to be able to balance the favourable and adverse effects.

The purpose of this study was to evaluate the effect of low (≤7.5 mg/d) and medium-dose (>7.5 mg/d) prednisone use in the preceding four months on the HOMA index and IR in a SLE cohort with a low-medium disease activity.

Materials and methods
Patients
We studied 128 patients with SLE who participated in a prior study on cardiovascular risk factors. Detailed characteristics and inclusion and exclusion criteria were previously described (7). This study was approved by the local ethics committee and all participants provided written informed consent.

Protocol and assessments
This was a cross-sectional study conducted over a 4-month period. Patients were evaluated using a standardised clinical interview, physical examination, laboratory test, and chart review. Participants were categorised in non-users (No PRD), low-dose (LD-PRD) (≤7.5 mg/day) or medium-dose (MD-PRD) (>7.5 mg/day) according to the received prednisone dose. All patients received prednisone at the time of inclusion and prednisone-equivalent calculation was not required. The majority of patients had been taking the same prednisone dose for the past 4 months at least. Only 5 patients were following a tapering regimen; for these subjects, the current prednisone dose was calculated as the mean daily prednisone dose during the past 4 months.

Definitions for body mass index (BMI), obesity, HTN, type 2 diabetes mellitus (DM), dyslipidaemia, smoking habits, sedentary lifestyle, family history of ASCVD, HOMA index, increased IR and MetS defined by the NCEP criteria (NCEP-MetS) were previously shown (7). A patient was considered as having MetS according to the WHO definition (WHO-MetS) when they fulfilled the following criteria: presence of DM or IR (in the present study defined as a HOMA index ≥2.51 that corresponded with the top quartile of SLE cohort) or impaired fasting glucose (≥110 mg/dl), plus at least any two of the following criteria: 1) waist-to-hip ratio >0.85 and/or BMI ≥30 kg/m²; 2) triglycerides (TG) ≥150 mg/dl and or high density lipoprotein (HDL) <40 mg/dl in men.
and <50 mg/dl in women; 3) systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg; 4) urinary albumin excretion >20 μg/min (14). Disease activity and accumulated organ damage were measured with the use of the SLE Disease Activity Index (SLEDAI) (15) and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) (16), respectively. The laboratory assessment was performed as described (7).

Statistical analysis
Data was presented as the median (interquartile range) for continuous variables and as a percentage (%) for categorical variables. Differences between continuous variables were tested for significance using the Mann-Whitney U-test or Student’s t-test as appropriate. Categorical data were analysed using Pearson’s chi-square test and odds ratios (OR) and 95% confidence intervals (CI) were calculated. In the first step, we compared the main characteristics of SLE patients categorised into 3 groups: No-PRD, LD-PRD and MD-PRD (Tables I and II). In the second step, we used a linear regression analysis (Spearman’s rho test) in order to determine the adjusted relationship between the current prednisone dose (Table III) and HOMA index and insulin levels (Table IV) with several parameters. All analyses used a two-sided 5% significance level. Statistical analyses were carried out using SPSS software for Windows (version 15.0. SPSS Inc., Chicago, USA).

Results
One hundred and twenty-eight patients with SLE (88% women) with a median age of 40 (32-52) years were studied. Demographic and clinical characteristics and therapies have been described in detail (7). The median SDI for the whole cohort was 1 (0-8) and the median SLEDAI value was 4 (0-18) indicating that most patients had inactive or moderately active disease status. Of the 128 patients, 41 (32%) did not take prednisone, 71 (55%) received low-dose prednisone (median 5 (2-5) mg), and 16 (12.5%) received medium-dose prednisone (Table I).
Table II. Renal involvement, inflammatory biomarkers, disease activity parameters and treatment in SLE patients categorised according to prednisone dose. Values are expressed as the median (interquartile range) unless stated otherwise.

<table>
<thead>
<tr>
<th>Renal involvement, %</th>
<th>No PRD n=41</th>
<th>LD-PRD n=71</th>
<th>MD-PRD n=16</th>
<th>p&lt;sup&gt;i&lt;/sup&gt;</th>
<th>p&lt;sup&gt;j&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal involvement</td>
<td>17</td>
<td>39</td>
<td>69</td>
<td>0.050</td>
<td>0.050</td>
</tr>
<tr>
<td>C reactive protein, mg/dl</td>
<td>0.2 (0.1-0.5)</td>
<td>0.2 (0.1-0.4)</td>
<td>0.2 (0.1-0.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate, mm/h</td>
<td>26 (17-36)</td>
<td>22 (12-33)</td>
<td>31 (18-75)</td>
<td>NS</td>
<td>0.049</td>
</tr>
<tr>
<td>Interleukin 6, pg/ml</td>
<td>2.5 (1-23)</td>
<td>2.3 (1-22)</td>
<td>4.2 (1.5-22)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Platelet count, (10&lt;sup&gt;9&lt;/sup&gt;/mm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>2.2 (1.8-2.6)</td>
<td>2.1 (1.9-2.6)</td>
<td>3.3 (2.4-4.0)</td>
<td>NS</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.8 (0.7-0.9)</td>
<td>0.8 (0.7-1.0)</td>
<td>0.7 (0.6-0.8)</td>
<td>NS</td>
<td>0.009</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>4.5 (4.3-4.6)</td>
<td>4.3 (4.1-4.6)</td>
<td>4.1 (3.8-4.5)</td>
<td>0.025</td>
<td>0.083</td>
</tr>
<tr>
<td>C3, mg/dl</td>
<td>100 (91-120)</td>
<td>96 (83-108)</td>
<td>88 (66-105)</td>
<td>0.004</td>
<td>0.049</td>
</tr>
<tr>
<td>C4, mg/dl</td>
<td>23 (18-28)</td>
<td>20 (14-25)</td>
<td>14 (9-22)</td>
<td>0.050</td>
<td>0.050</td>
</tr>
<tr>
<td>Homocysteine, μmol/l</td>
<td>13 (10-15)</td>
<td>13 (11-16)</td>
<td>13 (11-14)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anti dsDNA +ve, %</td>
<td>32</td>
<td>35</td>
<td>81</td>
<td>NS</td>
<td>0.001</td>
</tr>
<tr>
<td>SLEDAI</td>
<td>2 (1-4)</td>
<td>4 (2-7)</td>
<td>6 (4-12)</td>
<td>0.001</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Treatment, %

<table>
<thead>
<tr>
<th>NSAID</th>
<th>61</th>
<th>54</th>
<th>44</th>
<th>NS</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroxychloroquine</td>
<td>56</td>
<td>79</td>
<td>100</td>
<td>0.017</td>
<td>0.063</td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td>5</td>
<td>37</td>
<td>100</td>
<td>0.010</td>
<td>0.005</td>
</tr>
<tr>
<td>Current prednisone dose, mg/d</td>
<td>0</td>
<td>5 (2.5-5)</td>
<td>10 (10-12.5)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


<sup>i</sup> No PRD vs. LD-PRD groups; Student’s t-test for continuous variables.
<sup>j</sup> LD-PRD vs. MD-PRD groups; Mann-Whitney U-test for continuous variables.

Pearson’s chi-square test for categorical variables.

Univariate analysis

Demographics and metabolic differences. No significant differences were found between the No PRD and LD-PRD groups except for the fact that the first group was older, had higher levels of LDL-C, SBP and microalbuminuria. It is interesting of note that glucose, insulin, C-peptide, HOMA index and the frequency of increased IR were similar in both groups. In contrast, the MD-PRD group had significantly higher levels of insulin and C-peptide, and a higher HOMA index than patients from the LD-PRD group. In particular, increased IR was found to be present almost 3-fold more in the MD-PRD group than in the LD-PRD group (OR 5.8, 95% CI (1.7–20), p=0.007) (Fig. 1). Besides, the MD-PRD group was younger and the duration of disease and the age of SLE onset were lower than in the LD-PRD group. Likewise, microalbuminuria and creatinine levels were higher, probably as a result of the greater renal involvement in this group (Table II). On the other hand, no differences were found in the frequency of NCEP-MetS in the three groups. However, the prevalence of WHO-MetS tended to be higher in the MD-PRD group in relation to the LD-PRD group, but not high enough to reach statistical significance (19% vs. 10%, respectively; p=0.081) (Table I).

Treatments. Patients from the MD-PRD group received significantly more antihypertensives and statins than non-prednisone users, but no differences were found between the LD-PRD and MD-PRD groups (Table I). All patients who received medium-dose prednisone also took HCQ and immunosuppressive agents (8 azathioprine, median 100 mg/day; 7 mycophenolate mofetil, median 750 mg/day; 1 regular treatment with cyclophosphamide because of active lupus nephritis), in a greater proportion compared with patients from the other two groups (Table II).

Clinical and biological SLE-related factors. As expected, patients from the MD-PRD group had higher disease activity in comparison with patients from the other 2 groups. Thus, the MD-PRD group had significantly higher SLEDAI (but not SDI), ESR (but not CRP or IL-6 levels), platelet count, lower C3 and C4 serum levels, positive anti-DNA-
antibodies and tended to have a lower albuminemia ($p=0.083$) than the LD-PRD group.

**Linear regression analysis**

Daily prednisone dose correlated with the HOMA index, insulin and C-peptide levels even after simultaneous adjustment for sex, age, BMI, SLEDAI, ESR, renal involvement and the use of immunosuppressive agents. Conversely, prednisone did not correlate with ESR, CPR or IL-6 (Table III). On the other hand, SLEDAI or activity markers (ESR, C4, platelet count and anti-dsDNA antibodies) did not correlate with insulin or the HOMA index after adjusting for sex, age, BMI, and prednisone dose (Table IV). However, C3 significantly correlated with insulin and HOMA index not only after adjustment for the previous confounders (Table IV), but also after additional adjustment for ESR ($p=0.001$).

**Discussion**

The main finding of this study was that patients with SLE who were exposed daily to a prednisone dose >7.5 mg (median 10 mg/day) during the past 4 months, had greater IR and higher insulin levels than those patients who did not take prednisone or received low doses ($\leq$7.5 mg/day; median 5 mg/day). Moreover, levels of insulin and IR from non-prednisone users were similar to those patients taking low-dose prednisone, which suggests that at this dose, CS may not have an impact on IR in these patients.

Increased insulin levels and IR has been previously demonstrated in SLE patients (3, 4, 9). In addition, the presence of MetS (in which an insulin-resistant state exists) has been associated with arterial stiffness in SLE patients (7) and IR has been related to CAC in patients with rheumatoid arthritis (17). There are several mechanisms by which SLE could contribute to the impaired insulin sensitivity in these patients. These include obesity, systemic inflammation and medications used to control the disease activity.

Long-term CS use has been associated with weight gain and central obesity (18), which is considered to be an important source of pro-atherogenic inflammatory cytokines. (19). In SLE patients, obesity has been independently associated with inflammation markers such as CPR and IL-6, contributing significantly to the overall inflammation burden in these patients (20). Recently, it has been found that BMI is the major contributing factor to IR in patients with SLE (17). In our study, we also found a strong association between the HOMA index and BMI even after adjustment for sex, age, SLEDAI and current prednisone use ($r_s=0.460, p<0.001$) (data not shown). Likewise, increased IR was associated with obesity or 3.6, 95% CI 1.5–8.7, $p=0.007$) (data not shown). However, the increase in IR and hyperinsulinaemia found in the MD-PRD group in relation to the other two groups cannot be attributed to obesity since BMI, waist circumference and frequency of obesity were similar in all groups, probably because these prednisone doses were not high enough to cause a significant impact on weight and BMI (11, 12).

On the other hand, several studies have shown that inflammatory mediators are independently related to IR (21, 22). Recently, we found increased levels of CRP, IL-6 and fibrinogen in SLE patients with MetS compared with those without (7). In addition, Chung et al. found that the HOMA index positively correlated in a significant way with IL-6, TNF-α and ESR in RA patients, but only ESR showed this correlation in SLE patients (17). As expected, the MD-PRD group had more SLEDAI and...
activity markers and received more immunosuppressive agents than the other two groups (Table II). However, no correlation was found between insulin levels or the HOMA index and disease activity (SLEDAI) or inflammation state (including ESR – in contrast with the findings of Chung et al. (17), anti-dsDNA antibodies, C4, platelet count) after adjusting for sex, age and BMI (Table IV). Only C3 remained significantly associated even after adjusting for inflammatory or disease activity confounders. Moreover, although prednisone dose positively correlated with the HOMA index and insulin levels, no correlation were observed with inflammatory markers after adjusting for sex, age, BMI, SLEDAI, ESR renal involvement and immunosuppressive agents use (Table III). Finally, no differences were found between patients with SLEDAI <4 and SLEDAI ≥4 (median SLEDAI =4) in insulin levels, HOMA index and frequency of IR (data not shown). Considering all these findings it is unlikely that, in the context of low disease activity, increased IR, a higher HOMA index and higher insulin levels found in the MD-PRD group are fundamentally due to inflammation. On the other hand, in keeping with Posadas et al. (9) we found a significant independent association between the HOMA index and insulin levels and the prednisone dose. This relationship was still evident after adjustment for sex, age, BMI, SLEDAI and ESR. In contrast, El-Magadmi et al. (3) only found a weak association between insulin sensitivity and current steroid dose or steroid dose intake in the past 6 months; however, this study only included 44 SLE patients and perhaps it was not statistically powerful enough.

Interestingly, patients taking a medium dose of prednisone had increased IR and insulin levels compared with the other two groups; however increased IR was not associated with a higher prednisone dose or with current use of prednisone. A possible explanation for this apparent contradiction is that, since the pathogenesis of IR in SLE is multifactorial, the importance of CS in comparison with other factors such as obesity is probably relatively low and the potential effect of CS on insulin sensitivity may be overshadowed. In contrast, when patients were categorised according to their prednisone exposure, confounding factors like obesity are counterbalanced, prevailing the effect of CS. Hence, in the present study, SLE patients with increased IR had a higher BMI than SLE patients without (28 (24-32) vs. 25 (22-29), p=0.014). Conversely, as stated, BMI was similar in the No-PRD, LD-PRD and MD-PRD groups (Table I). Therefore, in this setting, CS could be a significant contributing factor for IR in the MD-PRD group in comparison with the other two groups.

With regard to the role of other therapies as the cause of possible bias, patients from the MD-PRD group received more HCQ and immunosuppressive agents than those from the other two groups. On the one hand, it has been reported that anti-malarials could reduce IR by increasing the half-life of the active insulin-receptor complex (23). On the other hand, since inflammation contributes to IR, the anti-inflammatory effect of immunosuppressive agents also may lead to lower IR. Therefore, the effect of both therapies, if any, would have been improving IR, and despite this, it was greater in the MD-PRD group.

With respect to the clinical significance of these results, it is noteworthy that in the general population, modest increases of insulin around 110 pmol/l (15 mU/l), similar to those observed in the MD-PRD group (median 13 mU/l), have been found to impair endothelium function, probably by increasing oxidant stress (24), which may constitute a potential link between hyperinsulinaemia and atherosclerosis in humans. Some major limitations of our study should be considered. Firstly, the number of patients included was relatively low (specially patients taking >7.5 mg/d of prednisona), which reduces the statistical power of the study. Secondly, we did not include a healthy control group and neither the impact of the SLE itself on IR nor the true prevalence of IR in SLE patients could be assessed. Thirdly, we did not consider the presence of anti-insulin antibodies, which have been found to be more prevalent in SLE (25), and could contribute to increase insulin levels and IR in these patients. Finally, given the cross-sectional design of the study, it is impossible to establish a true association between prednisone use and IR.

In conclusion, our study provides evidence that in patients with SLE, an average daily dose of prednisone >7.5 mg increased insulin levels and IR, whereas the impact of a prednisone dose ≤7.5 mg/d on these parameters was similar to that observed in non-prednisone users. These results may have clinical implications. We hypothesise that, with a dose ≤7.5mg/day, the anti-inflammatory action of prednisone could prevail over the proatherogenic effect, whereas at higher doses the opposite could occur. Thus, in a large, population-based study using a record linkage database, patients who received an average daily dose ≥7.5 mg of prednisone-equivalent were 2.5 times more likely to experience a cardiovascular event than patients who did not use CS, after adjustment for known covariates. In contrast, patients who took an average daily dose of <7.5 mg of prednisone-equivalent had a similar risk of suffering a cardiovascular event than non-users of CS (26). A large prospective study would be needed to confirm this hypothesis. Meanwhile, our results support the recommendation to keep the CS dose in SLE patients as low as clinically possible and withdraw it in all patients when this is feasible.

When higher doses are required, the extensive use of HCQ and the early addition of immunosuppressive agents like CS-sparing in order to achieve prednisone dose below 7.5 mg/d is strongly recommended.

Acknowledgment
We would like to thank Miss Ana Rosales for her invaluable assistance in organising the clinical records. We also would like to thank all our patients for their cooperation and interest in the present study.

References
2. GRUNDY SM, CLEEMAN JJ, DANIELS SR et
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