Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis

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Objective. Rheumatoid arthritis (RA) associates with increased cardiovascular morbidity and mortality that is due to both traditional and novel cardiovascular risk factors. Hypertension (HT), one of the most common risk factors for cardiovascular disease, is highly prevalent in RA. The effects of long-term glucocorticoid (GC) therapy on blood pressure have not been established yet. This study examined whether GC exposure associates with HT in patients with RA.

Methods. Four hundred consecutive RA patients with detailed clinical and laboratory assessments were categorized into three groups according to GC exposure: no or limited exposure (N/L-E); a low-dose (<7.5 mg) long-term exposure (LD/LT-E); and medium-dose (>7.5 mg) long-term exposure (MD/LT-E). The association of GC exposure with HT was evaluated using logistic regression analysis.

Results. HT was more prevalent in the MD/LT-E group (84.7%) than the LD/LT-E or N/L-E groups (70.7 and 67.3%, respectively, $P = 0.028$). Logistic regression revealed increased odds for HT when comparing MD/LT-E with N/L-E, after adjustment for HT risk factors [odds ratio (OR) = 2.57, 95% CI 1.01–6.56, $P = 0.049$] and RA disease characteristics (OR = 3.64, 95% CI: 1.36–9.77, $P = 0.01$).

Conclusions. MD/LT GC exposure associates with a very high prevalence of HT. This appears to be independent of other risk factors for HT or of channelling bias due to disease severity, even though the latter cannot be excluded given the cross-sectional nature of our study. RA patients in this GC exposure group should be particularly targeted for early identification and aggressive management of HT.

**KEY WORDS:** Glucocorticoids, Steroids, Hypertension, Cardiovascular disease, Rheumatoid arthritis.

Introduction

Patients with RA experience an increased burden of cardiovascular disease (CVD) and reduced life span compared with the general population [1]. The reasons for the increased CVD remain a matter of extensive research and include a clustering of classical, novel (serum uric acid) and RA-specific CVD risk factors [2–4]. Hypertension (HT) is one of the most important modifiable classical CVD risk factors [5] in the general population and is very common in patients with RA [6]. In the INTERHEART study [7], HT accounted for 18% of the population attributable risk of a first myocardial infarction (MI). HT increases the risk of CVD both in the general population [8] and in RA patients [9].

In current rheumatology practice, short-term glucocorticoids (GCs) are frequently used as ‘bridge therapy’ while waiting for onset of action of DMARDS, or for disease flares, and are thought to exert their beneficial anti-rheumatic effect at least for up to 6 months [10]. A recent review [11] suggests that GCs given in addition to standard therapy can substantially reduce the rate of erosion progression in RA. Long-term use in RA is more controversial because of waning effectiveness and increasing risk of adverse effects [12], although they may be required for severe systemic disease.

Seven decades ago, Cushing [13] was the first to report a link between excess plasma cortisol levels and HT in a patient with Cushing’s syndrome. Since then, several studies have shown that increased cortisol secretion and action, even within the normal range, is associated with HT [14, 15]. However, the effect of exogenous long-term GC use on blood pressure (BP) has not yet been established despite decades of clinical use.

In the present cross-sectional study, we investigated the association between GC exposure and the presence of HT in patients with RA, and examined whether this association is independent of other risk factors for HT and RA disease severity.

Patients and methods

Recruitment and detailed characteristics of the cohort have been described in previous papers [6]. The original study had approval by the local Research Ethics Committee and Research and Development approval and all participants gave their written informed consent according to the Declaration of Helsinki.

GC dose [in all cases oral daily prednisolone (milligrams) (ODP)] and exposure time were recorded and patients were categorized using standardized nomenclature [16] into: low dose (ODP < 7.5), medium dose (7.5 ≤ ODP ≤ 30) and high dose (30 < ODP); short-term (<3 months), medium-term (3–6 months) or long-term (>6 months) exposure. Patients were categorized into three groups according to dose and time of GC exposure: no or limited exposure (N/L-E) (those who never received steroids or had been exposed for <3 months at the time of assessment); low-dose, long-term GC exposure (LD/LT-E) (patients who received <7.5 ODP for >6 months) and medium-dose long-term exposure (MD/LT-E) (patients on ≥7.5 ODP for >6 months). HT was defined as a systolic BP ≥ 140 and/or diastolic BP ≥ 90 and/or the use of anti-hypertensive medications [17].

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate whether each parameter followed a normal distribution. Values were expressed as mean ± s.d., median (interquartile range) or percentages, as appropriate. Comparisons were performed by analysis of variance, Kruskal–Wallis and chi-squared test for normally distributed, non-normally distributed and categorical variables, respectively. Binary logistic regression analysis was used to...
evaluate the independence of the association between GC exposure and HT status. Differences were considered significant at a P-value of <0.05 (two-tailed). All analyses were carried out using SPSS 14.0 (SPSS Inc., Chicago, IL, USA).

Results

Just under one-third of the patients (131/400, 32.8%) were currently receiving ODP. Of them, 60 (45.8%) were on low-dose GC and 71 (54.2%) on medium dose; no patient was on high-dose GC. Two hundred and eighty-one patients (70.6%) belonged to the MD/LT-E group (18%), one (2.28, respectively (Table 1). This was probably mirrored in the rarer use of sulphasalazine as a DMARD in the MD/LT-E (18.6%) and LD/LT-E (19%) groups than the N/L-E (34.2%) group (P = 0.009). There were no significant differences in the use of any other anti-rheumatic medications or in some of the risk factors traditionally associated with HT, including HT history, dyslipidaemia, insulin resistance (IR), obesity or renal dysfunction.

Independence of the association between GC exposure and HT

In order to assess the independence of the apparently significant association between MD/LT-E and HT in this RA population, two binary logistic models were created to adjust for potential confounders (Table 2). In the first model (Model A), adjustments were made for all common HT risk factors and associations traditionally associated with HT, including HT history, dyslipidaemia, insulin resistance (IR), obesity or renal dysfunction.
assessed in this study: the odds ratio (OR) for HT, when comparing the MD/LT-E with the N/L-E group, remained significantly increased [OR=2.57 (1.01–6.56), \( P = 0.049 \)]. In the second model (Model B), further adjustment was made for RA characteristics (DD, HAQ and joint surgery); the association remained independent and significant [OR=3.64 (1.36–9.77), \( P = 0.011 \)] (Table 2).

### Discussion

Despite decades of GC use in the routine clinical setting, relatively little is known about their effects on BP, particularly in patients with RA. The present cross-sectional, observational study suggests that RA patients exposed to medium ODP doses (≥7.5 mg) for long periods (>6 months) are significantly more likely to be hypertensive than RA patients who have no or limited exposure, or receive low-dose (<7.5 mg) ODP. The main limitation of this study is its cross-sectional nature: because of this, causality is not proven and directionality of associations must be viewed with caution. Other potential limitations include the difficulty of assessing the exact extent of GC exposure time and exposure dose and the fact that this study is based on a secondary care cohort and thus generalizability of the results should be cautiously approached. On the other hand, this is the only study in decades aiming to address this question in patients with RA, in a large sample with very detailed clinical and laboratory characterization, allowing adjustment for many potential confounders. This reduces, but does not eliminate, the increased risk of channeling bias in interpreting the association between GC and HT.

Most of the evidence for an association between GC and HT arises from studies on endogenous cortisol levels. Morning plasma cortisol concentrations are higher in hypertensive than in normotensive subjects [14]. Young adults with a predisposition to HT have also been shown to have higher plasma cortisol concentration [18] and secretion rates [19] than those without this trait, while a positive correlation has even been found between plasma cortisol and white-coat BP effect [20]. It remains unclear, whether long-term exogenous GCs used for therapeutic purposes associate with HT.

The most relevant study was performed 26 yrs ago, when Jackson and colleagues [21] studied the effects of corticosteroid therapy on BP, in 129 asthmatic and 66 RA patients: they concluded that long-term (>1 yr) ‘low-dose’ (<20 mg daily) GCs do not lead to BP increases, and that significant HT may be better explained by age and initial BP than by the use of GCs. However, new thresholds were recently set to define ‘low’, ‘medium’ and ‘high'-dose prednisolone [16]. Patients in the study of Jackson et al. [21] could belong both to the ‘modern’ low- or medium-dose category and this may have influenced the results. Another study from the early 1970s [22] reported that radiologically visible arteriosclerosis in the ankle joint region in RA patients on long-term GC was three times more frequent than in RA patients not receiving GC or in healthy controls. There was no information on GC dose and duration, and no adjustment for age, disease activity or severity. In a recent population-based study, Wei et al. [23] reported that therapeutic use of supraphysiological doses of GC may be associated with increased rates of MI, stroke, heart failure and all-cause mortality. These outcomes were compared between 68,781 patients receiving ≥7.5 mg/day of prednisolone or equivalent for more than a year and 82,202 non-GC users. Adjustments were made for treatment of classical CVD risk factors (e.g. anti-hypertensive or lipid-lowering therapy), but not for risk factors per se; such statistical adjustment may not have taken into account patients who are undiagnosed or untreated and thus at a higher risk for CVD [24]. Notwithstanding this, the authors concluded that there is an independent association between GC usage and CVD, which cannot be explained by increased prevalence of any of the traditional CVD risk factors. This concurs with the findings of the present study, which suggests an increased HT burden only in the supraphysiological (≥7.5 mg), long-term GC exposure group, which could explain part of the excess CVD mortality in this group [7, 9].

An important question is whether the association between GC and HT reflects a direct effect or simply mirrors an association between HT and the underlying severe disease for which GCs were prescribed in the first place (channeling bias). Classical CVD risk factors alone cannot explain the increased CVD in RA [25] and many studies suggest that clinical and laboratory features of high inflammatory disease activity or severity (i.e. the type of disease that is often treated with GC) associated with cardiovascular events and mortality [26, 27]. In the present study, statistical adjustment for RA parameters (DD, HAQ, joint surgery) led to a strengthening of the association between medium-dose, long-term GC usage and HT. DD was significantly higher and could have contributed to the increased prevalence of HT in the LD/LT-E and MD/LT-E groups compared with the N/L-E one. However, adjustment for DD in our multivariable model did not alter the significant association between HT and GC exposure in the MD/LT-E group. Disease activity [disease activity score (DAS)-28] was not considered a confounder since there were no statistically significant differences among the three groups in the univariable analysis. The latter could be attributed to GC treatment itself, which leads to improvement of DAS28 scores. However, HAQ and joint surgery are good indicators for severe disease and are not influenced as much by current GC use, therefore adjustment for these variables may alleviate the channeling bias in the present study. The increase in the adjusted OR (Model B) suggests that the possible deleterious direct effects of GC on BP may be, to a certain extent, counterbalanced by a beneficial effect on inflammatory load and disease severity. This can be addressed in longitudinal studies of long-term prospective cohorts.

If there is a direct effect of long-term supraphysiological GC on BP, in RA, the question arises as to what mechanisms may mediate this. The prevalence of arterial plaques and incompressible arteries has been reported to be higher among RA patients in the highest tertile of cumulative GC exposure (>16,338 mg prednisolone), than in GC-unexposed patients [28]. Previous studies have demonstrated that arterial incompressibility is usually a manifestation of medial arterial calcification [29], which is also known as Mockenberg’s sclerosis and is present in two-thirds of RA patients on long-term GCs [22]. Many studies have established the association of arterial stiffness and the subsequent development of HT in the general population [30]. All the above studies suggest a potential link, leading from increased cumulative GC exposure to arterial stiffness and subsequent HT. Another intriguing hypothesis is that GC-induced osteoporosis and arterial calcification share pathogenic mechanisms [31]. There are several other mechanisms that have been suggested to be implicated in the pathogenesis of cortisol-induced HT. Increased peripheral vascular sensitivity to adrenergic agonists [32], activation of renal
GC exposure associates with hypertension in RA

mineralocorticoid receptors by cortisol in the setting of reduced 11β-hydroxysteroid dehydrogenase-2 activity [33] or GC excess, and prostaglandin production inhibition [34] are some of the suggested mechanisms in the literature. None of these mechanisms have been addressed in patients with RA and they could form the basis of future studies.

In summary, the present study is the first to suggest a potential direct link between MD/LT GC usage and HT in patients with RA. This may partially explain the increased CVD in long-term GC-exposed RA patients and indicates the need for further prospective clinical, epidemiological and mechanistic studies. In the meantime, this group of RA patients should be specifically targeted for early identification and, if necessary, aggressive management of HT.

**Rheumatology key messages**

- Long-term, ≥7.5 mg daily, glucocorticoid use associates with HT in RA.
- Such patients require frequent monitoring and aggressive management of their HT.

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