Glucocorticoids and Insulin Sensitivity in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To evaluate the effects of glucocorticoids on cardiovascular (CV) risk in rheumatoid arthritis (RA).

Methods. We recorded demographic, clinical, disease outcome, and treatment variables in 92 consecutive RA patients who were not taking lipid-lowering or antidiabetic medications. Fasting blood tests were taken for determination of lipids, ultra sensitive C-reactive protein (CRP), rheumatoid factor, insulin, and glucose. Insulin sensitivity was determined using the Quantitative Insulin Sensitivity Check Index (QUICKI).

Results. Seventy-four (80%) patients were women, 80 Caucasian, 9 Asian, 2 of mixed ancestry and 1 Black. Their mean (95% confidence interval, CI) age, disease duration, and followup duration at our clinic were 56 (54-58), 11 (9-13) and 6 (5-6) years, respectively. Thirty-seven (40%) patients had received oral prednisone [cumulative dose 4.8 (2.0-8.5) g; duration one month to 20 years], and all patients had received pulsed (intraarticular, intramuscular, and/or intravenous) methylprednisolone [cumulative dose 2.0 (1.6-2.6) g]. Glucocorticoids were not associated with obesity, hypertension, or dyslipidemia. Having taken prednisone and high yearly frequencies of pulsed glucocorticoid administrations were associated with decreased insulin sensitivity ($p < 0.05$). After controlling for body mass index, ever having taken prednisone and high doses of pulsed glucocorticoids were independently associated with decreased insulin sensitivity ($p < 0.05$).

Conclusion. Previous exposure to oral prednisone and high doses of pulsed glucocorticoids were associated with decreased insulin sensitivity in RA. Since decreased insulin sensitivity is an independent risk factor for CV disease, glucocorticoids may contribute to the excess CV event rates in RA. (J Rheumatol 2004;31:867-74)

Key Indexing Terms:
RHEUMATOID ARTHRITIS GLUCOCORTICOIDS CARDIOVASCULAR RISK

The previously reported increased risk for cardiovascular (CV) events in rheumatoid arthritis (RA)[1,2] was recently confirmed in 3 large studies[3-5], 2 of which were prospective[3,4]. The frequency of acute myocardial infarction was increased up to 4-fold.

The pathogenesis of atherosclerosis and its complications in RA await elucidation[1]. However, systemic inflammation is strongly implicated. The extent of radiological joint damage explained about one third of the variance of ultrasonographically determined carotid artery intima media thickness, a marker of atherosclerosis, in 138 RA patients[6].

Since glucocorticoids decrease systemic inflammation and retard radiographic progression in RA[7], they may be expected to have a beneficial effect on CV disease. However, glucocorticoids adversely affect traditional CV risk factors including lipid and glucose metabolism, blood pressure, and body weight[8]. Moreover, the use of glucocorticoids in autoimmune disorders was shown to be associated with endothelial dysfunction, an initial step in atherosclerosis[9]. In one study, the use of prednisone predicted CV events in RA[10] and more recently, glucocorticoid therapy in RA was associated with electrocardiographic QT dispersion, a reliable predictor of CV events[11].

We hypothesized that glucocorticoids contribute to traditional CV risk factors in RA independent of other disease related variables. Since the mechanisms of action, benefits, and side effects of oral physiological dose (e.g. ≤ 4 mg prednisone daily), oral pharmacological dose (e.g. > 4 mg prednisone daily) and pulsed (intraarticular, intramuscular, intravenous) glucocorticoids are reportedly dissimilar in RA[12,13], we further hypothesized that these forms of glucocorticoid administration have different effects on CV risk profiles.

MATERIALS AND METHODS

Patients. Ninety-two consecutive patients followed for at least 6 months at one of our clinics (Milpark Hospital) were enrolled in our study. This was the number of patients seen over a 2-month period. Exclusion criteria comprised the use of lipid-lowering or antidiabetic agents. All patients met the American College of Rheumatology criteria for RA[14].

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Methods. We recorded the following variables: age, gender, smoking history, ethnic background, disease duration, duration of followup at our clinic, current use of glucocorticoids and disease modifying antirheumatic drugs (DMARD), body mass index (BMI) (kg/m^2), Health Assessment Questionnaire Disability Index, visual analog scales for pain, global disease activity according to the patient (patient disease activity) and the physician (physician disease activity), respectively, and 36 joint counts for tenderness, swelling, and deformity[15,16]. Blood pressure was measured on 3 occasions and patients were considered hypertensive if the lowest measurement was > 140/90 mm Hg or if patients were taking antihypertensives. Additionally, fasting blood tests were taken between 8 AM and 10 AM for determination of the following: high sensitivity C-reactive protein (CRP) (mg/l) [immuno-turbidimetric assay on Olympus OSR6185, Olympus Diagnostics GmbH (Irish Branch), Lismeehan, O'Callaghan's Mills, County Clare, Ireland]; rheumatoid factor (latex); plasma glucose (mmol/l); serum insulin (Abbott, Chicago, IL, USA); total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides (Olympus Diagnostics), and low density lipoprotein (LDL) cholesterol (Randox Laboratories Ltd., Crumlin, UK).

Insulin sensitivity was estimated by the Quantitative Insulin Sensitivity Check Index (QUICKI) using the formula 1 ÷ log insulin (uU/ml) × log glucose (mg/dl)[17]. Normal values for QUICKI were obtained in 94 healthy adults (70 women; 85 Caucasian, 6 Asian, 2 Black, and 1 of mixed ancestry; mean (range) age 48 (25-81) years who had no core features of the insulin resistance/metabolic syndrome comprising an increased waist circumference (> 88 cm in women and > 102 cm in men), blood pressure ≥ 130/ ≥ 85 mmHg, fasting plasma glucose ≥ 6.1 mmol/l and decreased fasting HDL cholesterol (< 1.3 mmol/l in women and < 1.0 mmol/l in men) or increased triglyceride concentrations (≥ 1.7 mmol/l)[18]. The mean (95% confidence interval, CI; range) QUICKI was 0.400 (0.393-0.407; 0.338-0.542) in these controls and values below the lower 95% CI level (0.393) were considered reduced. Diabetes was diagnosed in patients with a fasting plasma glucose ≥ 7 mmol/l as recommended by the World Health Organization[19]. All diabetic patients in the present cohort were treated with dietary intervention only. In keeping with reported recommendations, an LDL cholesterol > 3 mmol/l, HDL cholesterol < 1.3 mmol/l in women and < 1.0 in men and triglycerides ≥ 1.7 mmol/l were considered abnormal[18]. A body mass index (BMI) > 27.5 kg/m^2 was considered elevated.

Information on previously used glucocorticoids and DMARD therapy as well as the CRP at enrolment in our clinic were obtained from review of the patients' medical records. At enrolment in our clinic, all patients had been systematically questioned about DMARD therapy and the doses and duration of glucocorticoids previously used. After enrolment, details of glucocorticoid and DMARD therapies were recorded prospectively.

For study purposes, the following glucocorticoid therapy variables were recorded: current prednisone exposure, current prednisone dose, previous exposure to prednisone, previous exposure to pharmacological doses of prednisone (> 4 mg per day), and the duration of the latter; the total number, mean yearly frequency, and mean dose of pulses used; and finally, the cumulative oral, pulsed, and total glucocorticoid quantities were calculated. The only oral agent used was prednisone and only parenteral used agent was methylprednisolone. The use of nonsteroidal antiinflammatory agents and aspirin was not recorded. CRP had been measured in all patients at enrolment in our clinic. This was on average 6 years (followup duration at our clinic) prior to the performance of other laboratory tests in the present cohort. At that time, high sensitivity CRP testing was not available to us and enrolment CRP had been measured using a routine CRP testing method, namely the immuno-turbidimetric assay on Olympus AU600.

The study was approved by the Ethic Committees for Research on Human Subjects (Medical) of the University of Witwatersrand and the Milpark Hospital, respectively.

Statistical analyses. Data were analyzed using Wilcoxon rank sum tests and simple and multiple regression analyses. Results were expressed as mean (95% CI) unless indicated otherwise.

RESULTS

Patient characteristics. Of the 92 patients, 74 (80%) were women, 80 Caucasian, 9 Asian, 2 of mixed ancestry, and 1 Black. Their mean (95% CI) age, disease duration, and followup duration at our clinic were 56 (54–58), 11 (9–13), and 6 (5–6) years, respectively. Seventy-three (79%) patients tested positive for rheumatoid factor.

Cardiovascular risk factors. The cardiovascular risk factors that were recorded are presented in Table 1. A high BMI, hypertension, and dyslipidemia were each found in more than 50% of the patients. Decreased insulin sensitivity was recorded in 72 (78%) of the patients, of whom 12 had type 2 diabetes mellitus. The mean age in the controls was 8 years lower compared to the patients. However, neither in the patients nor in the controls was age related to the QUICKI (R = –0.005, p = 0.96 and R = 0.0389, p = 0.71, respectively). The distribution of the QUICKI in the 92 patients is shown in Figure 1. The fasting insulin (uU/ml) and QUICKI were 10.0 (8.1–11.9) and 0.358 (0.349–0.368), respectively.

Glucocorticoid and DMARD therapy. The main characteristics of glucocorticoid and DMARD therapy are presented in Table 2. Thirty-seven (40%) patients had received oral prednisone. Eighteen (20%) patients were on prednisone at the time of completion of the study while the dose taken was ≤ 4 mg daily in 16. The duration of oral glucocorticoid exposure in these 37 patients ranged from 1 month to 20 years. Pulsed (intraarticular, intramuscular, and/or intravenous) methylprednisolone had been administered to all patients. At enrolment in our clinic, only 17 (18%) patients were using DMARD [methotrexate (n = 9); sulfasalazine (n = 8); chloroquine (n = 5); parenteral gold (n = 1); penicillamine (n = 1)] as compared to 84 (91%) patients at the time of completion of the study [methotrexate (n = 77); chloroquine (n = 44); minocycline (n = 19); sulfasalazine (n = 6); azathioprine (n = 6); parenteral gold (n = 1), and leflunomide (n = 4).

Relationships between glucocorticoid therapy and cardiovascular risk factors. The relationships between glucocorticoid therapy characteristics and insulin sensitivity are

Table 1. Cardiovascular risk factors in 92 patients with RA.

Cardiovascular Risk Factor	Patients, n (%)
Current smokers	26 (28)
BMI > 27.5 kg/m^2	53 (58)
Hypertension	57 (62)
LDL cholesterol > 3 mmol/l	65 (71)
Low HDL cholesterol* and/or high triglycerides**	55 (60)
Decreased insulin sensitivity	72 (78)
Diabetes	12 (13)
Current CRP > 10 mg/l	26 (28)
CRP > 10 mg/l at enrolement in our clinic	55 (60)

BMI: body mass index; CRP: C-reactive protein. * < 1.3 mmol/l in women and < 1.0 mmol/l in men, ** ≥ 1.7 mmol/l.

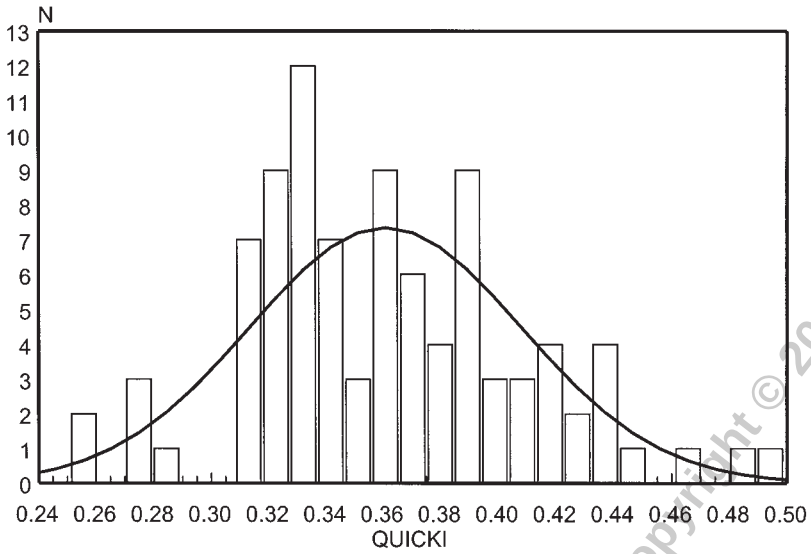

Figure 1. Histogram showing the distribution of the QUICKI in 92 patients with RA.

Table 2. Glucocorticoids and DMARD in 92 patients with RA. Results expressed as mean (range) unless otherwise noted.

Treatment Characteristics	
Cumulative oral GC (g) (n = 37, 40%)	4.8 (0–107.7)
Currently taking prednisone, n (%)	18 (20)
Current prednisone dose, mg	0.6 (0–7)
Ever taken prednisone, n (%)	37 (40)
Ever taken prednisone > 4 mg/d, n (%)	27 (29)
Duration of prednisone > 4 mg/d, yr	0.8 (0–20)
Cumulative pulsed GC, g (n = 92, 100%)	2.0 (0.06–11)
Pulses per patient	8.8 (1–39)
Yearly frequency of pulses	1.9 (0–8)
Mean pulse doses, mg	230 (60–665)
Total cumulative glucocorticoids, g	7.3 (0.06–111.3)
Total number of DMARD used	3.5 (1–8)
Currently used DMARD	1.7 (0–3)
DMARD used at enrolment in our clinic	0.3 (0–3)

DMARD: disease modifying agents; GC: glucocorticoids.

Table 3. Correlations between insulin sensitivity and glucocorticoid treatment.

Treatment Characteristic	R	p
Cumulative oral GC (0–107.7 g)	0.027	0.797
Current pred exposure (0 = not taking pred; 1 = pred)	0.034	0.751
Current pred dose (0–7 mg daily)	–0.056	0.594
Pred exposure (0 = never taken pred; 1 = ever taken pred)	–0.207	0.047
Exposure to > 4 mg pred daily (0 = ever taken pred > 4 mg/day 1 = never taken pred > 4 mg/day)	–0.076	0.469
Duration of pred > 4 mg/day (0–20 yrs)	–0.183	0.080
Cumulative pulsed GC (0.06–11g)	–0.111	0.292
No. of pulses (1–39)	–0.058	0.585
Pulse frequency (0–8 per yr)	–0.225	0.031
Mean pulse dose (60–665 mg)	–0.186	0.077
Cumulative total GC (0.06–111.3 g)	0.010	0.924

GC: glucocorticoids; pred: prednisone.

shown in Table 3. Ever having taken prednisone and high yearly frequencies of pulsed glucocorticoid administrations were significantly associated with decreased insulin sensitivity. The distribution of insulin sensitivity in patients who had never taken prednisone versus patients who had taken prednisone is presented in Figure 2. The mean (95% CI) QUICKI was 0.366 (0.355–0.377) and 0.348 (0.332–0.363) in patients who had never taken prednisone versus patients who had taken prednisone, respectively. This difference was significant at p = 0.01 by Wilcoxon rank sum test. The QUICKI values in the individual patients who had never taken prednisone versus those who had taken prednisone are shown in Figure 3. The mean (95% CI) fasting insulin concentrations were 12.4 (8.9–16.0) and 8.6 (6.4–10.8) (p = 0.026) in patients having received oral glucocorticoids and patients who had never used oral glucocorticoids, respectively. By comparison, the mean (95% CI) fasting insulin level in control subjects was 4.6 (4.2–5.0).

Using simple linear regression models with elevated BMI, hypertension, elevated LDL cholesterol, reduced HDL cholesterol, and/or elevated triglycerides being entered as dependent variables, none of the glucocorticoid therapy characteristics were significantly associated with the respective cardiovascular risk factors (results not shown).

To establish whether or not the association between glucocorticoid therapy and decreased insulin sensitivity was related to confounding variables, we compared the baseline features, recorded outcome variables, and DMARD therapy

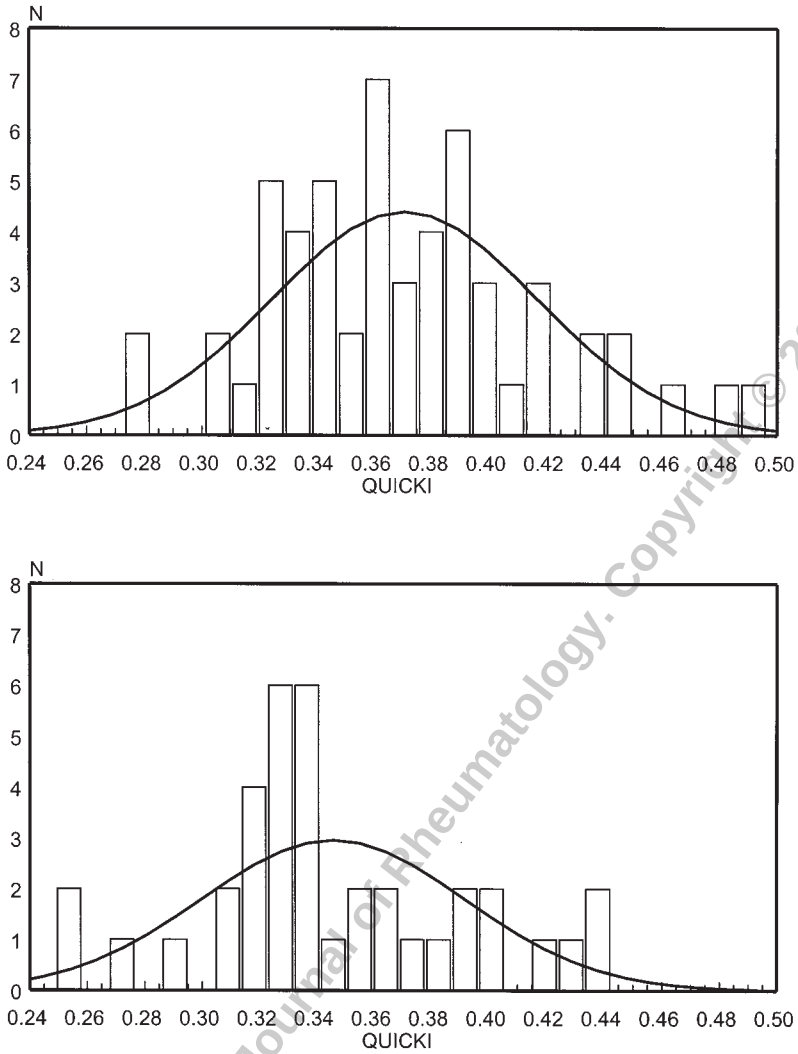

Figure 2. Histograms showing the distribution of the QUICKI in patients with RA who never received oral glucocorticoids (upper diagram) and those who had (lower diagram).

in patients with decreased insulin sensitivity, with the respective variables in patients with normal insulin sensitivity (Table 4). The BMI was higher in patients with decreased insulin sensitivity ($p = 0.002$). This confirms that the cutoff for normal insulin sensitivity determined in controls was effective at identifying patients with the metabolic syndrome feature being excess weight. Indeed, overall, patients with normal insulin sensitivity had a normal BMI while those with reduced insulin sensitivity had an elevated BMI. The relationship between excess weight and insulin resistance in RA has been reported[20-22]. In view of the above, we repeated the previously performed simple linear regression analyses (Table 3, column 2), now each time adding the BMI as a covariate into each model. In these multiple regression analyses, having taken prednisone and high mean pulsed glucocorticoid doses were independently predictive of reduced insulin sensitivity. These results are shown in Table 5. The other glucocorticoid therapy characteristics were not independently associated with insulin sensitivity (results not shown).

DISCUSSION

Although glucocorticoids have been used to treat RA patients for over 50 years, their optimal role remains a controversial issue[8]. Glucocorticoids may particularly benefit patients when prescribed as bridge therapy upon initiation of DMARD and while awaiting a disease activity suppressant effect of the latter[8,23]. On the other hand, the side effects associated with their longterm usage remain a matter of considerable concern. Glucocorticoid related osteoporosis in RA is the most extensively documented side effect[8]. However, although RA patients experience an up to 4-fold increased risk for CV events[1-5] and the observation that glucocorticoids may adversely affect CV risk[8], their

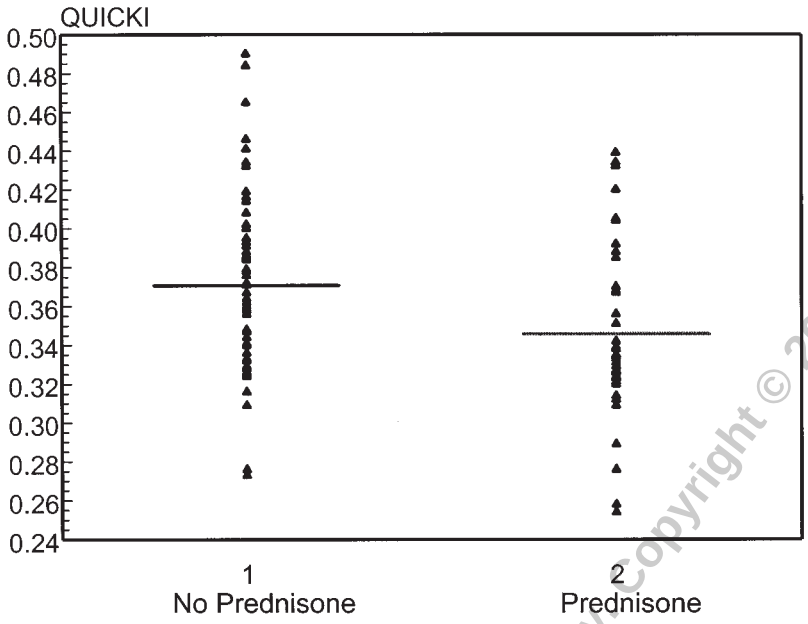

Figure 3. Individual QUICKI values in patients with RA who had never received prednisone and in those who had.

potential role in comorbid CV disease in RA awaits elucidation. Glucocorticoids are relatively inexpensive and were being prescribed in 59% of patients in a recently reported study[24].

The gold standard for the assessment of insulin sensitivity is the euglycemic hyperinsulinemic clamp technique[17,25]. However, the QUICKI has been reported to be a reliable surrogate marker of insulin sensitivity[17,25]. By using the lower 95% CI of the QUICKI obtained in healthy controls as a cutoff for the presence of reduced insulin sensitivity, subjects with metabolic syndrome features could be identified reliably[25] and this was confirmed in our study as

Table 4. Baseline features, disease outcome variables, and DMARD in patients with normal and decreased insulin sensitivity[15], respectively. Results expressed as mean (range).

Variable	Normal IS, n = 20 (22%)	Decreased IS, n = 72 (78%)
Age, yrs	59 (54–64)	55 (53–58)
Women, n (%)	15 (75)	59 (82)
Caucasian, n (%)	20 (100)	59 (82)
Disease duration, yrs	12.2 (7.9–16.5)	10.6 (8.4–12.7)
Followup duration, yrs	5.7 (4.8–6.5)	5.5 (4.0–7.1)
BMI, kg/m^2	23.2 (21.3–25.1)	27.5 (26.2–28.2)
Smoking, n (%)	5 (25)	21 (29)
HAQ-DI, range 0–3	0.739 (0.390–1.088)	0.690 (0.503–0.877)
No. of tender joints, range 0–36	3.0 (0.9–5.2)	5.4 (3.4–7.4)
No. of swollen joints, range 0–36	2.7 (1.1–4.4)	3.2 (2.0–4.5)
No. of deformed joints, range 0–36	6.0 (2.4–9.6)	3.7 (1.9–5.6)
Patient disease activity, range 0–10*	3.5 (1.8–5.1)	3.6 (2.8–4.4)
Physician disease activity, range 0–10*	2.7 (1.0–4.3)	3.6 (2.0–3.5)
Pain (range 0–10)*	3.7 (2.0–5.3)	3.6 (2.8–4.4)
Rheumatoid factor positive, n (%)	14 (70)	59 (82)
Current CRP, mg/l	17.3 (1.2–33.4)	13.2 (6.7–19.8)
CRP (mg/l) at enrolment in our clinic	27.0 (15.2–39.0)	30.6 (17.9–43.4)
Total DMARD taken	3.9 (2.9–4.8)	3.4 (3.0–3.8)
No. of DMARD currently taken	1.3 (0.9–1.7)	1.7 (1.5–1.9)

HAQ-DI: Health Assessment Questionnaire Disability Index; CRP: C-reactive protein. * results obtained from visual analog scales.

Table 5. Predictors of insulin sensitivity in 92 patients with RA. Pulse dose values are given in g due to the small regression coefficients.

Variables entered	Analysis I B (95% CI)	p	Analysis II B (95% CI)	p
Pred exposure (0 = never taken pred, 1 = ever taken pred)	–0.017 (–0.033 to –0.001)	0.045		
Mean pulse dose (0.06–0.665 g)			–0.08 (–0.1 to –0.01)	0.018
BMI (14.5–41.5 kg/m^2)	–0.0035 (–0.005 to –0.001)	< 0.0001	–0.004 (–0.005 to –0.002)	< 0.0001

Pred: prednisone.

related to excess weight. Another surrogate marker of insulin resistance is the homeostasis model assessment (HOMA). We did not utilize the HOMA in our study since the QUICKI is significantly better correlated with insulin sensitivity from glucose clamp studies than is the HOMA[17]. The mean QUICKI in our controls was slightly higher than that reported in healthy subjects in previous studies (0.382 and 0.366)[17,25]. This confirms the statement made by Hrebicek, *et al* that a normal QUICKI range needs to be established for each laboratory with an appropriate control group because of significant interlaboratory variations in insulin determinations and/or possible differences in various populations[25]. Also, our control group was larger than the ones in previous studies and our controls were selected on the basis of stricter criteria based upon the recently reported features of the metabolic syndrome by the National Cholesterol Education Program[18].

In our cohort, oral glucocorticoids had been used in only 37 (40%) patients while DMARD were extensively administered. All patients had received DMARD and 84 (91%) were on these agents at the time of completion of the study. Our main finding was that previous glucocorticoid therapy was associated with reduced insulin sensitivity. The use of glucocorticoids in RA may merely reflect more aggressive disease[1,26]. However, after controlling for potential confounding variables, ever having taken oral prednisone and high doses of pulsed glucocorticoids were independently predictive of reduced insulin sensitivity. Glucocorticoid therapy was not associated with obesity, hypertension, or dyslipidemia. We could not show an association between glucocorticoids and the presence of diabetes mellitus (results not shown), but the number of patients investigated was probably too small to establish such a relationship since only 12 patients had this complication.

Insulin resistance predicts the development of type 2 diabetes mellitus[27]. More importantly in the present context, in the Quebec Study, an 18% increase in fasting insulin concentration was independently associated with a 1.7-fold increased risk for ischemic heart disease[28]. Our finding that the mean fasting insulin concentrations were 2.2-fold higher in RA patients than in controls suggests a potential role for reduced insulin sensitivity in CV disease in RA. Insulin sensitivity was significantly more reduced in patients who had received oral glucocorticoids compared to those who had not been exposed to such therapy. Indeed, glucocorticoids commonly affect insulin sensitivity and this has been reported extensively[29-32]. This adverse effect of glucocorticoids is reportedly irreversible in about 50% of patients despite dose reduction or drug withdrawal[29]. Glucocorticoids reduce the binding affinity of insulin receptor, antagonize insulin-mediated inhibition of hepatic glucose release through stimulation of the expression of phosphoenolpyruvate-carboxykinase and glucose-6-phosphatase, and decrease glucose utilization in muscle[29,30]. Glucocorticoids induce insulin resistance and also decrease insulin secretion in cases of glucocorticoid related diabetes[31,32]. Both phenomena are partially reversible with the use of thiazolidinediones, agents that enhance insulin sensitivity[31]. In a recent study of 10 healthy subjects, dexamethasone 4 mg daily for 4 days drastically affected glucose tolerance and insulin sensitivity[32]. These effects were completely prevented when the thiazolidinedione troglitazone was administered concurrently with dexamethasone[32]. The relationship between the use of glucocorticoids and insulin sensitivity in our cohort is in contrast to the reported effects of 20 mg prednisone used for one week in active RA. Here, insulin sensitivity improved, a finding that was related to a reduction in systemic inflammation (the acute phase response)[33]. Taken together, short term and longterm oral glucocorticoids may have contrasting effects on insulin sensitivity in RA. The reversibility of glucocorticoid induced insulin resistance in RA upon glucocorticoid withdrawal and/or with the use of insulin sensitizing agents needs further study.

We recently reported a median (interquartile range) reduction in insulin resistance of 36% (26-61%) over 3 months in 22 patients with active RA upon treatment with DMARD despite the use of pulsed glucocorticoids as bridge therapy at the time of DMARD initiation[23]. In that report, the patients were younger (median age 50 years), their disease duration shorter (median 5.5 years), their disease activity higher (median CRP 22 mg/l), and the methylprednisolone doses lower (median 200 mg) compared to the present study. The present investigation does suggest that high doses of pulsed glucocorticoids have the potential to adversely affect glucose metabolism in RA.

Our study has the following limitations. Only 18 (20%) of our patients were taking prednisone and only 2 patients were taking pharmacological doses at completion of our study. Our study was therefore underpowered to address the effects of currently taken oral glucocorticoids at high doses on CV risk factors including insulin sensitivity. However, in a recent investigation, the use of 10 mg prednisone daily for 2 years in RA was associated with a 3 kg weight gain and a significant increase in mean serum glucose levels of 16%[7]. In our experience, the use of high dose oral glucocorticoids is rarely necessary in RA when DMARD are used extensively as in our cohort. While glucocorticoid therapy was prospectively recorded during a mean of 6 years' followup in the present cohort, there was a potential for recall bias at enrolment in our clinic. Finally, although exposure to oral glucocorticoids and high doses of pulsed glucocorticoids were independently associated with reduced insulin sensitivity, the cross-sectional design of our study precludes the establishment of a definite cause-and-effect relationship.

In a recent study of 20 patients with autoimmune disease, the use of glucocorticoids was associated with a significant mean decrease of 43% in forearm blood flow to reactive hyperemia, which is indicative of endothelial dysfunction[9]. This complication was related to the generation of reactive oxygen species by the respective agents and was markedly attenuated when reassessed 2 hours after administration of 2 grams of vitamin C[9]. The contribution of glucocorticoids to CV events and the role of preventive measures such as the use of antioxidants, dietary intervention, and exercise in order to enhance insulin sensitivity in RA patients treated with glucocorticoids require further study.

In conclusion, we found that previous exposure to oral glucocorticoids and high doses of pulsed glucocorticoids in RA were associated with decreased insulin sensitivity independent of other disease related variables. Since insulin resistance is an independent predictor of CV events[28], glucocorticoids may contribute to the excess of CV disease-related complications reported in RA.

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