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ORIGINAL ARTICLE

Effect of acute and chronic glucocorticoid therapy on insulin sensitivity and postprandial vascular function

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Summary

Objective Postprandial hyperglycaemia is associated with increased arterial stiffness and cardiovascular events. Low-dose prednisolone causes insulin resistance that typically manifests as postprandial hyperglycaemia. We investigated whether prednisolone causes postprandial vascular dysfunction in a cohort of patients with rheumatoid arthritis.

Design An open interventional and cross-sectional study was undertaken.

Patients and measurements Eighteen subjects with rheumatoid arthritis who had not taken oral glucocorticoids for ≥6 months were studied before and after prednisolone 6 mg/day for 7 days to determine the acute effects of prednisolone. Pre-prednisolone data were compared to 18 subjects with rheumatoid arthritis taking long-term (>6 months) prednisolone (6·5 ± 1·8 mg/day) to assess the chronic effects of prednisolone. Augmentation index (by applanation tonometry) and reactive hyperaemia index (by peripheral artery tonometry) were measured before and after a mixed-meal (10 kcal/kg, 45% carbohydrate, 15% protein, 40% fat). Insulin sensitivity was estimated by the Matsuda index and sympathetic nervous system activity from urinary noradrenaline excretion.

Results Matsuda index was lower after acute (2·0 ± 1·0 *vs* 3·6 ± 1·1, $P = 0{\cdot}01$) and chronic (1·9 ± 1·0 *vs* 3·6 ± 1·1, $P = 0{\cdot}04$) prednisolone. Postprandial augmentation index was lower after acute prednisolone (2551 ± 197 *vs* 2690 ± 272% *min, $P \leq 0{\cdot}001$), but not chronic prednisolone. There were no significant differences in reactive hyperaemia index with acute or chronic prednisolone. Noradrenaline excretion was lower after acute (54 ± 8 *vs* 93 ± 23 nmol/6 h, $P = 0{\cdot}02$), but not chronic, prednisolone.

Conclusions Prednisolone-induced insulin resistance is not associated with postprandial vascular dysfunction in patients with rheumatoid arthritis. Reduced sympathetic activity may contribute to the reduction in postprandial arterial stiffness with acute prednisolone.

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Introduction

Glucocorticoids are anti-inflammatory agents that are widely used to treat a range of inflammatory and autoimmune diseases. Despite an expanding range of therapeutic options, the prevalence of glucocorticoid use is increasing.[1] Although high-dose glucocorticoids are often needed acutely, daily prednisolone-equivalent doses of less than 10 mg are usually prescribed as long-term therapy.[1]

While high-dose glucocorticoid therapy is associated with an increased risk of cardiovascular disease, the effect of low-dose prednisolone on cardiovascular risk is uncertain.[2] Epidemiologic studies, which can be confounded by indication bias, have reported conflicting results.[3,4] The sample size and duration of randomized-controlled studies are insufficient to assess cardiovascular events.[5,6] Lacking definitive data, assessments of vascular function may provide important insight into the cardiovascular effects of low-dose prednisolone and clarify the risks of using glucocorticoids to treat chronic inflammatory disease.

Augmentation index is a measure of left ventricular afterload that is predominantly determined by arterial stiffness.[7] A higher augmentation index indicative of increased arterial stiffness is associated with an increased risk of cardiovascular disease, independent of traditional cardiovascular risk factors. Arterial stiffness is affected by vessel wall structure, but is also dependent

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on autonomic tone and endothelial function. Studies in healthy adults have shown impairment in microvascular function with low-dose prednisolone.[8] However, long-term prednisolone did not increase carotid intima media thickness or cause endothelial dysfunction in patients with rheumatoid arthritis (RA),[9] and in patients with polymyalgia rheumatica there was a fall in fasting augmentation index after 4 weeks of prednisolone.[10]

It is important to consider that these vascular effects of prednisolone were observed in fasting patients.[9,10] We previously reported that low-dose prednisolone predominantly causes postprandial hyperglycaemia.[11] In patients with type 2 diabetes mellitus or impaired glucose tolerance, when insulin resistance results in postprandial hyperglycaemia it is more strongly associated with cardiovascular events,[12] and arterial stiffness,[13] than when insulin resistance causes fasting hyperglycaemia. Furthermore, vascular dysfunction in these patients may only manifest during the postprandial period.[14,15]

We hypothesized that, similar to its adverse effects on blood glucose concentration, prednisolone-induced insulin resistance would predominantly adversely affect postprandial vascular function. As such, the aim of this study was to investigate the effect of low-dose prednisolone on postprandial glycaemia, insulin sensitivity and postprandial arterial stiffness in patients with RA. We also investigated whether changes in autonomic nervous system activity or endothelial function underlie any changes in arterial stiffness.

Materials and methods

Subjects and study design

Subjects aged 50 years or older with RA were recruited from the rheumatology outpatient clinic at Repatriation General Hospital, Adelaide, Australia. We studied 18 subjects who had not been administered any oral glucocorticoids for at least 6 months (non-GC users) and 18 subjects taking a stable continuous oral prednisolone dose of 4–10 mg/day for at least 6 months (GC users). The two groups were matched for age and sex. Non-GC users were studied before and after a 7-day course of oral prednisolone 6 mg daily to determine the acute effects of prednisolone. Baseline data from non-GC users were compared with data from chronic GC users to determine the chronic effects of prednisolone. Subjects with atrial fibrillation, Raynaud's phenomenon, on oral hypoglycaemic medications, insulin or beta blockers were excluded from the study. The study was approved by the Southern Adelaide Clinical Human Research Ethics Committee, Flinders Medical Centre, and all subjects provided written informed consent in accordance with the Declaration of Helsinki.

Study protocol

Subjects attended the Endocrine Research Unit at Repatriation General Hospital at 08:30 h after a 12-h overnight fast. All subjects took their regular medications in the morning prior to arrival, including prednisolone. Basic anthropometric measures were recorded. At each visit, after resting supine for a 20-min acclimatization period, subjects underwent fasting assessment of vascular function. An intravenous cannula was then inserted and baseline blood samples were collected to measure glucose, insulin, C-peptide and non-esterified fatty acid levels (NEFA). A mixed-meal was then administered over 15 min (10 kcal/kg body weight, 45% carbohydrate, 40% fat and 15% protein), and further blood samples for glucose, insulin, C-peptide and NEFA were collected at 30-min intervals for 120 min. Vascular function was reassessed after the mixed-meal in a standardized order.

Pulse wave analysis

The augmentation index was calculated by pulse wave analysis. Applanation tonometry was performed by one operator (AR) with a SphygmoCor device (AtCor Medical, New South Wales, Australia) and a high-fidelity micromanometer (SPC-301; Millar Instruments, TX, USA). Six measurements in the fasting state and three measurements at each specified postprandial time point were performed and averaged. The quality control indices within the SphygmoCor device software were used to verify recorded waveforms. If the quality index was <80%, the waveform was discarded and the measurement repeated. To correct for the effect of pulse rate, augmentation index results were normalized for a heart rate of 75 beats per min (AIx75). The day-to-day intra-class correlation for AIx75 for this operator is 0·97. The area under the curve (AUC) for AIx75 over 2 h was calculated to estimate postprandial arterial stiffness.

Autonomic nervous system activity

Urinary noradrenaline excretion was measured during the 6-h study period by liquid chromatography/mass spectrometry to estimate sympathetic nervous system activity. The coefficient of variation (CV) for urinary noradrenaline measurement is 5·1% at 300 nmol/l.

Spontaneous baroreceptor sensitivity, which predominantly reflects parasympathetic nervous system activity, was calculated by the sequence method using a Taskforce Hemodynamic Monitor 3040i (CNSystems, Graz, Austria).[16] A continuous electrocardiogram recording and "flying V" finger cuff for non-invasive measurement of beat-by-beat arterial pressure were placed on the subject, allowing simultaneous computer analysis of heart rate and blood pressure variability. After subjects had rested supine for 10 min, baroreceptor sensitivity was assessed over a 20-min period.

Peripheral arterial tonometry

Peripheral arterial tonometry was performed using an Endo-PAT 2000 device (Itamar Medical, Caesarea, Israel) to estimate endothelial function. After a baseline pulse amplitude measurement was obtained from both hands, local ischaemia to the arm was induced by inflating a blood pressure cuff to suprasystolic pressures for 5 min. The pulse amplitude response to hyperaemia is recorded electronically in both fingers (the non-occluded arm serves as control). The time period between 90 and 150 s after

deflation was used for automated calculation of the reactive hyperaemia index.[17] The average day-to-day CV for reactive hyperaemia index at our institution is 11·4%.[18]

Insulin sensitivity and secretion

Whole blood glucose was measured at the bedside immediately after venesection on an in-house glucose analyser (YSI 2300 STAT Plus; Yellow Springs Instrumentation, Ohio, USA) by an immobilized glucose oxidase method. Insulin and C-peptide were measured by radioimmunoassay (EMD Millipore, Toronto, Ontario, Canada). Quality control results were within one standard deviation of the mean at all concentrations. Insulin sensitivity was estimated by the composite insulin sensitivity index (Matsuda index),[19] and insulin secretion at baseline and each 30-min time point by the C-peptide deconvolution method.[20] Glucose-sensitive insulin secretion was then calculated by dividing the AUC for insulin secretion over 2 h by the AUC for blood glucose over 2 h.

Physical activity

Physical activity was assessed using the Modified Baecke Questionnaire.[21] The questionnaire is designed to estimate habitual physical activity in the elderly, and is a composite score based on household activity, sports and exercise and other leisure activities. Higher levels of physical activity are reflected by a higher score.

Other laboratory analysis

C-reactive protein was measured using a Tinaquant immunoturbidimetric assay (Roche Diagnostics GMBH, Mannheim, Germany) on a Roche Modular Analyser (Hitachi High-Technologies Corporation, Tokyo, Japan). The limit of detection was 0·3 mg/l. The between-run CV was 3·6% at a CRP of 3·9 mg/l and 2·3% at a CRP of 49·5 mg/l. NEFA concentrations were estimated by enzyme colorimetry using a Beckman Synchron CX5 analyser (WAKO NEFA C kit, Denver, CO, USA).

Statistical analysis

Statistical analysis was performed using IBM SPSS version 20 for Windows (IBM, New York, USA). A P-value of <0·05 was considered statistically significant. Subject characteristics are presented as mean ± standard deviation except characteristics that were not normally distributed, which are expressed as median (interquartile range). All other data are presented as mean ± standard error of mean. Changes in variables in non-GC users after 7 days prednisolone were analysed using paired t-tests. Hereafter in the manuscript, these results are reported as the acute effects of prednisolone. GC users were compared with baseline data from non-GC users using unpaired t-tests if normally distributed or Mann–Whitney U-tests if the distribution was not normal. Differences between these two groups are reported in the manuscript as the chronic effects of prednisolone.

The primary end-point is change or difference in the AUC for AIx75. In the acute study, a sample size of 18 subjects has >80% power to detect a 500%*min change in the AUC AIx75 (assuming a SD of 700%*min). In the chronic study, a sample size of 18 subjects per group has >80% power to detect a 680%*min difference in the AUC AIx75 (assuming a SD of 700%*min).

Results

Subject characteristics

GC users were taking a mean prednisolone dose of 6·5 ± 1·8 mg/day, with a mean duration of continuous prednisolone therapy of 62 ± 62 months. There were no significant differences in sex distribution, age, body mass index, height, C-reactive protein, physical activity score, use of disease-modifying antirheumatic drugs or history of hypertension or ischaemic heart disease between GC and non-GC users (Table 1).

Carbohydrate metabolism

Fasting glucose (5·3 ± 0·3 *vs* 4·6 ± 0·1 mmol/l, $P = 0·02$) and glucose AUC over 2 h (844 ± 58 *vs* 733 ± 27 mmol/l*min, $P = 0·03$) were higher after acute prednisolone. There were no significant differences in fasting (4·9 ± 0·2 *vs* 4·6 ± 0·1 mmol/l, $P = 0·20$) or glucose AUC over 2 h (822 ± 40 *vs* 733 ± 27 mmol/l*min, $P = 0·07$) with chronic prednisolone, although the higher glucose AUC with chronic prednisolone approached statistical significance. The Matsuda index was significantly lower after both acute ($P = 0·01$) and chronic ($P = 0·04$) prednisolone (Fig. 1a). There were no significant differences in insulin secretion with either acute or chronic prednisolone (Fig. 1b).

Non-esterified fatty acids

There was no significant difference in fasting (0·7 ± 0·1 *vs* 0·6 ± 0·1 meq/l, $P = 0·24$) or NEFA AUC over 2 h (39·5 ± 3·5

Table 1. Subject characteristics

	Non-GC users (n = 18)	GC users (n = 18)	P-value
Female, n (%)	12 (67)	12 (67)	1·00
Age (years)	64 ± 7	66 ± 7	0·33
BMI (kg/m^2)	28·1 ± 5·2	27·9 ± 6·1	0·95
Height (m)	1·65 ± 0·08	1·68 ± 0·07	0·24
C-reactive protein (mg/l)*	2·4 (1·1-4·5)	1·6 (0·5-7·6)	0·44
Physical activity score	12·8 ± 5·7	10·5 ± 5·5	0·22
DMARDs (n)	11	9	0·50
Ischaemic heart disease (n)	1	1	1·00
Hypertension (n)	5	4	0·70
Statins (n)	5	3	0·69
Anti-hypertensives (n)	5	3	0·69

Data are mean ± SD unless otherwise stated, * = median (interquartile range), n = number of patients with specified variable. GC = glucocorticoid, BMI = body mass index, DMARDs = disease-modifying antirheumatic drugs.

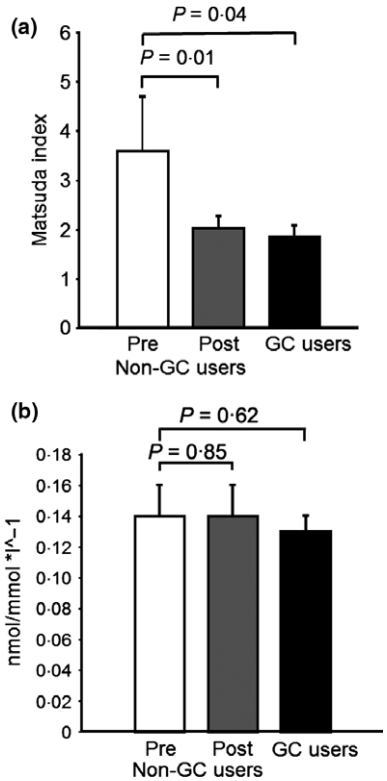

Fig. 1 Insulin sensitivity (Matsuda index, a) and glucose-sensitive insulin secretion (b) in 18 subjects with rheumatoid arthritis who do not take oral glucocorticoids (non-GC users) before (white bars) and after (grey bars) 7 days prednisolone and 18 subjects with rheumatoid arthritis on long-term prednisolone (GC users, black bars). Data are mean ± SEM.

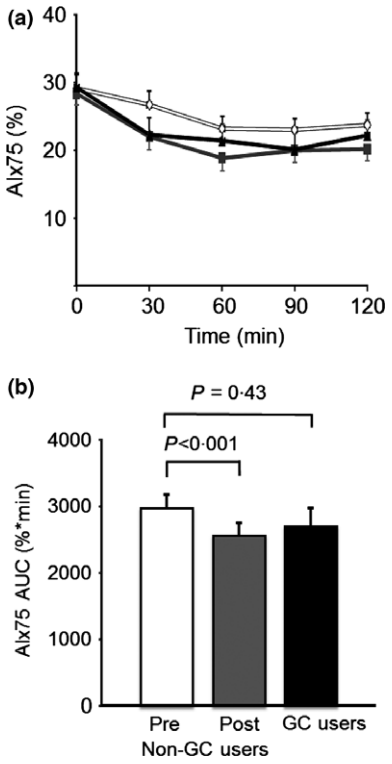

Fig. 2 Time course for augmentation index (AIx75) over 2 h (a) and area under the curve for augmentation index (AIx75 AUC) over 2 h (b) in 18 subjects with rheumatoid arthritis who do not take oral glucocorticoids (non-GC users) before (white line) and after (grey line) 7 days prednisolone and in 18 subjects with rheumatoid arthritis on long-term prednisolone (GC users, black line). Data are mean ± SEM.

vs 34·5 ± 3·1 meq/l*min, $P = 0{\cdot}12$) after acute prednisolone. Fasting (1·0 ± 0·1 *vs* 0·6 ± 0·1 meq/l, $P = 0{\cdot}002$) and NEFA AUC over 2 h (47·1 ± 3·9 vs 34·5 ± 3·1 meq/l*min, $P = 0{\cdot}02$) were significantly higher in patients taking chronic prednisone.

Pulse wave analysis

There were no significant differences in fasting AIx75 with either acute (28·0 ± 1·7 *vs* 29·2 ± 2·0%, $P = 0{\cdot}46$) or chronic (29·1 ± 2·1 *vs* 29·2 ± 2·0%, $P = 0{\cdot}98$) prednisolone. Following the meal, there was a fall in AIx75 in all groups indicating a reduction in arterial stiffness (Fig. 2a). There was a greater reduction in the AUC for AIx75 after acute prednisolone (Fig. 2b, $P < 0{\cdot}001$). The AUC for AIx75 was not significantly different with chronic prednisolone (Fig. 2b).

Autonomic nervous system activity

There was a reduction in urinary noradrenaline excretion after acute prednisolone (Fig. 3a, $P = 0{\cdot}02$). Urinary noradrenaline excretion was not significantly different with chronic prednisolone (Fig. 3a). There were no significant differences in fasting (data not shown) or post-meal (Fig. 3b) baroreceptor sensitivity with acute or chronic prednisolone.

Peripheral arterial tonometry

There were no significant differences in fasting reactive hyperaemia index with either acute (2·2 ± 0·2 *vs* 2·4 ± 0·1, $P = 0{\cdot}33$) or chronic (2·3 ± 0·2 *vs* 2·4 ± 0·1, $P = 0{\cdot}90$) prednisolone. Following the meal, there was a fall in reactive hyperaemia index in all groups indicating a reduction in endothelial function (Fig. 4). There was no significant difference in the post-meal reduction in reactive hyperaemia index after acute prednisolone (Fig. 4). In chronic prednisolone users, the post-meal fall in reactive hyperaemia index was approximately 60% of that in non-GC users, but this difference was not statistically significant (Fig. 4, $P = 0{\cdot}09$). There was not a significant correlation between the post-meal change in reactive hyperaemia index and NEFA AUC ($r = 0{\cdot}26$, $P = 0{\cdot}13$).

Discussion

This study assessed the effects of acute and chronic low-dose prednisolone on carbohydrate metabolism and fasting, and postprandial vascular function in patients with RA. We found that low-dose prednisolone increased postprandial glucose concentration secondary to a reduction in insulin sensitivity. However, this was not associated with adverse changes in vascular function.

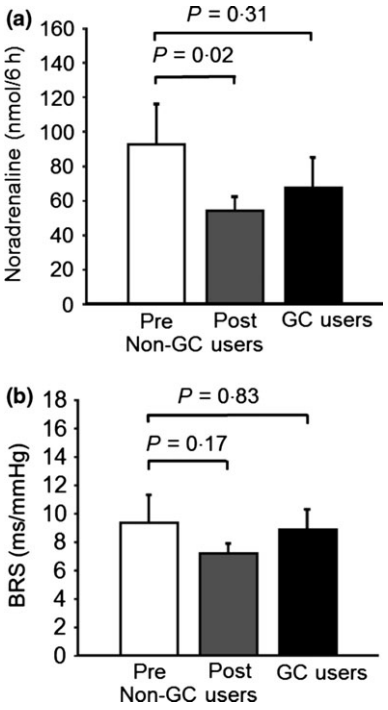

Fig. 3 Urinary noradrenaline excretion (a) and postprandial baroreceptor sensitivity (b) in 18 subjects with rheumatoid arthritis who do not take oral glucocorticoids (non-GC users) before (white bars) and after (grey bars) 7 days prednisolone and 18 subjects with rheumatoid arthritis on long-term prednisolone (GC users, black bars). Data are mean ± SEM.

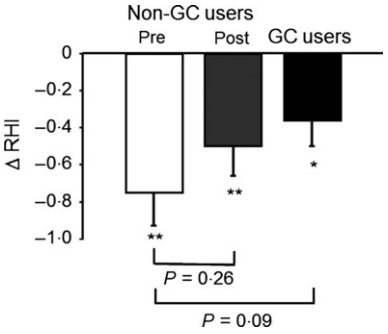

Fig. 4 Post-meal change in reactive hyperaemia index (RHI) in 18 subjects with rheumatoid arthritis who do not take oral glucocorticoids (non-GC users) before (white bars) and after (grey bars) 7 days prednisolone and 18 subjects with rheumatoid arthritis on long-term prednisolone (GC users, black bars). Data are mean ± SEM. $^{*}P < 0{\cdot}05$ for within group change in RHI after the meal, $^{**}P < 0{\cdot}005$ for within group change in RHI after the meal.

High-dose glucocorticoids can cause hyperglycaemia because they reduce insulin sensitivity and secretion.[22] However, fewer studies have investigated the effects of lower glucocorticoid doses on carbohydrate metabolism. One cross-sectional study reported no significant differences in insulin sensitivity and secretion between patients with RA on long-term low-dose prednisolone *vs* prednisolone naive patients.[23] In contrast, we found that low-dose prednisolone in patients with inflammatory arthritis reduced hepatic and peripheral insulin sensitivity, assessed using gold standard metabolic techniques.[24] In this study, we employed a physiologic (mixed-meal) test and also found that low-dose prednisolone reduced insulin sensitivity, with no significant change in insulin secretion. These data suggest that, even at low doses, prednisolone has an adverse effect on carbohydrate metabolism.

As glucocorticoid receptors are present in vascular endothelial cells, prednisolone could affect vascular function directly. Alternatively, prednisolone could alter vascular function indirectly secondary to reducing insulin sensitivity. Vascular tissues are an important physiological target for insulin,[25] and insulin resistance is an established risk factor for cardiovascular disease.[26] Acutely, insulin resistance can increase arterial stiffness because of reduced signalling through the phosphatidyl ionositol-3 kinase pathway leading to reduced nitric oxide-mediated vasodilatation. Chronically, enhanced stimulation of the mitogen-activated protein kinase pathway by hyperinsulinaemia can cause vascular smooth muscle proliferation and excessive production of inflammatory cytokines, contributing to accelerated atherosclerosis.[27] We hypothesized that adverse changes in arterial stiffness would be greater in patients taking chronic than acute prednisolone, because of the combination of attenuated and enhanced signalling via the phosphatidyl ionositol-3 kinase and mitogen-activated protein kinase pathways respectively.

Patients with insulin resistance have an attenuated postprandial reduction in augmentation index.[15] We hypothesized that prednisolone-induced insulin resistance would result in similar adverse changes in vascular function. However, contrary to our hypothesis, acute prednisolone use was associated with a greater postprandial fall in augmentation index. In patients on long-term prednisolone there was no suggestion of a higher postprandial augmentation index indicative of increased arterial stiffness. We previously reported that fasting augmentation index was lower in hypopituitary patients after a 7-day increase in glucocorticoid dose.[28] These data suggest that low-dose glucocorticoids do not induce deleterious changes in arterial stiffness that will increase cardiovascular risk.

The autonomic nervous system is an important regulator of cardiovascular function. A prednisolone dose of 20 mg/day for 7 days was reported to reduce sympathetic nervous system activity,[29] with *in vitro* studies suggesting that this effect is mediated by non-genomic pathways.[30] We found that lower prednisolone doses are also acutely associated with reduced sympathetic nervous system activity. Urinary noradrenaline excretion was also 27% lower in patients on long-term prednisone but this difference was not statistically significant. Reduced sympathetic nervous system activity is a likely mechanism to explain a reduction in augmentation index with low-dose prednisolone.

There were no significant changes in spontaneous baroreceptor sensitivity with either acute or chronic low-dose prednisolone. These findings in patients with RA are similar to those in young healthy men,[31] and hypopituitary patients,[28] exposed to mild glucocorticoid excess. Measurements of baroreceptor sensitivity using the sequence method predominantly reflect

parasympathetic, and not sympathetic, nervous system activity.[16] Our findings suggest that the fall in augmentation index with low-dose prednisolone is not mediated by an increase in parasympathetic nervous system activity.

In this study, neither acute nor chronic low-dose prednisolone significantly affected fasting reactive hyperaemia index, a marker of endothelial function. There were conflicting data on the effects of glucocorticoids on fasting endothelial function. There were no significant changes in flow-mediated dilatation with short-term prednisolone in healthy adults,[32] or long-term prednisolone in patients with RA.[9] In contrast, there was a dose-dependent reduction in microcapillary recruitment with acute prednisolone in healthy young adults,[8] and a reduction in fasting reactive hyperaemia index after 7 days of an increased glucocorticoid replacement dose in hypopituitary patients.[28] The contrasting findings in different studies may reflect different methods of assessment of endothelial function, glucocorticoid dose and formulation or susceptibility to the effects of glucocorticoids in different patient groups.

Reactive hyperaemia index falls after a glucose load in patients with insulin resistance and post-glucose load hyperglycaemia, but not in patients with normal glucose tolerance.[14] However, despite reduced insulin sensitivity and consequent postprandial hyperglycaemia, there was no change in the postprandial reduction in reactive hyperaemia index after acute prednisolone. Furthermore, there was a trend to an attenuated postprandial fall in reactive hyperaemia index in patients on long-term prednisolone suggestive of better endothelial function. This occurred despite higher NEFA concentrations in patients on chronic prednisolone, which have been associated with postprandial endothelial dysfunction and atherosclerosis.[33] One possible explanation for these findings is that low-dose prednisolone acts directly on the endothelium to improve endothelial function. Alternatively the anti-inflammatory effect of prednisolone in the long-term could improve endothelial function, similar to other disease-modifying drugs.[34] Although, there were no significant differences in C-reactive protein or in the use of disease-modifying antirheumatic drugs between the two groups, it is possible that prednisolone affected a component of the inflammatory cascade that modulates endothelial function. Whatever the mechanism, our study suggests that in contrast to the general population, prednisolone-induced postprandial hyperglycaemia in subjects with rheumatoid arthritis is not associated with postprandial endothelial dysfunction.

This study does not provide direct evidence of the effect of low-dose prednisolone on cardiovascular events. However, augmentation index,[8] reactive hyperaemia index,[17] and baroreceptor sensitivity,[16] are all well-validated markers of cardiovascular risk independent of traditional cardiovascular risk factors. The effect of low-dose prednisolone on all 3 markers of cardiovascular risk was either neutral or in a direction associated with reduced cardiovascular events. Given the lack of direct evidence of the cardiovascular effects of low-dose prednisolone, this study provides some confidence that low-dose prednisolone can be used to attenuate disease progression in this patient group without increasing cardiovascular risk.

The strengths of this study include that we simultaneously assessed carbohydrate metabolism and fasting and postprandial vascular function in our patient groups. However, we acknowledge this study has limitations. Firstly, in this study with a relatively small sample size, the acute study analysed using paired t-tests has greater statistical power than the chronic study, which was analysed using appropriate statistical tests for independent groups. A lack of statistical significance in the chronic study may reflect its lesser statistical power rather than attenuation of the effect of prednisolone. As such, our findings should not be interpreted as indicating that the acute and chronic effects of prednisolone on augmentation index and noradrenaline secretion differ. However, it is relevant that the direction of change in all measures of vascular function in the cross-sectional study was similar to the acute study. This suggests that chronic prednisolone does not exert opposite (adverse) effects on vascular function. Secondly, inherent in any cross-sectional study is the possibility that an unmeasured variable affected results. However, the groups were well matched for a number of key variables (Table 1). Thirdly, calculation of a Matsuda index from a mixed-meal test is not as well validated as from a glucose load. However, calculation of a Matsuda index from a mixed-meal test classifies differences in insulin sensitivity in groups of healthy adults[19] and prednisolone-induced changes in insulin sensitivity[35] similarly to a euglycaemic-hyperinsulinaemic clamp. Finally, our study does not investigate the effect of prednisolone doses above 10 mg/day, which have been associated with a greater risk of cardiovascular events.[4]

In summary, we have demonstrated that low-dose prednisolone treatment in patients with RA was associated with a higher postprandial glucose secondary to a reduction in insulin sensitivity. However, these changes in carbohydrate metabolism were not associated with adverse effects on markers of arterial stiffness, endothelial function or autonomic nervous system activity. In fact, arterial stiffness was acutely reduced by low-dose prednisolone, which is likely to be secondary to a prednisolone-induced reduction in sympathetic nervous system activity. Our findings suggest that in contrast to the relationship in the general population, postprandial hyperglycaemia may not be a marker of cardiovascular risk in patients with RA on low-dose prednisolone.

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Disclosure

The authors have no disclosures to declare.

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