

Rheumatology 2017;56:494–495

doi:10.1093/rheumatology/kew421

Advance Access publication 10 December 2016

Timing of glucocorticoid administration: a cross-sectional survey of glucocorticoid users in an online social network for health**Rheumatology key message**

- The timing of glucocorticoid administration varies significantly in patients, potentially influencing effectiveness and side effects.

SIR, there is a growing body of evidence that the timing of glucocorticoid (GC) administration may be important in reducing symptoms of RA, with evening or night-time doses being shown to reduce morning stiffness [1–3]. A modified-release prednisolone, which is taken in the evening and releases prednisolone 4 h later to coincide with the body's circadian rhythm of naturally occurring cortisol, has been shown to reduce morning stiffness compared with standard prednisolone taken in the morning [4] and placebo [5]. There is emerging evidence that steroid receptors are differentially expressed in different organs at different times of the day [6], therefore the timing of treatment may affect side-effect profiles. However, it is often recommended that GCs should be taken in the morning due to side effects such as adrenal suppression [7]. It is not known what time patients actually take GCs, therefore the aim of this study was to determine the time people take their GCs.

A short survey of GC users was conducted through Healthunlocked.com, an online social network for health. When users visited a post with the title word 'steroid' or the tags 'glucocorticoid', 'prednisolone', 'prednisone',

'steroid' or 'dexamethasone' the survey popped up for completion. The survey started with a screening question to determine whether respondents were current GC users or had used GCs in the last month. If so, the survey continued with six further questions about the respondent's age, gender, GC use and the timing of GC administration. The survey was live for 3 months. During the survey, respondents were asked, 'Do you take your daily dose of steroids once per day, or do you split the dose over two or more times through the day?' Followed by 'What time do you normally take your steroid tablets?' Respondents could indicate the time(s) using a 24 h clock. The study received ethics approval from the University of Manchester Research Ethics Committee (reference 15496). As respondents did not provide identifiable information, informed consent was not required.

At the end of the 3 month survey period 637 respondents had answered the dose and timing questions. Of those, 598 (93.9%) had one dose per day and 39 (6.1%) had two or more doses per day. The majority [$n = 557$ (93.1%)] of single-dose respondents had their dose in the morning, though there was variation within this. A total of 145 (24.2%) respondents usually took their dose between 6 and 7.59 a.m., 320 (54%) between 8 and 9.59 a.m. and 62 (10%) between 10 and 11.59 a.m. (Table 1).

Similarly, for those who indicated having multiple doses, there were patterns in the times GCs were taken, but still variation within these patterns. For example, of those taking two doses, the majority had their first dose in the morning and the second in the afternoon, but the time of the first and second dose ranged from 12 a.m. to 8.59 p.m. and 8 a.m. to 11.59 p.m., respectively (Table 1).

To the best of our knowledge, this is the first study reporting the times people take GCs. The results show that

TABLE 1 Time of GC administration by the number of doses per day ($n = 637$)

Time	Single dose, n (%)	Two doses per day, n (%)		Three doses per day, n (%)		
		Dose 1	Dose 2	Dose 1	Dose 2	Dose 3
12–5.59 a.m.	18 (3)	2 (6.5)	–	–	2 (25)	1 (12.5)
6–7.59 a.m.	145 (24.3)	8 (25.8)	–	2 (25)	–	–
8–9.59 a.m.	320 (53.5)	16 (51.6)	1 (3.2)	6 (75)	–	–
10–11.59 a.m.	62 (10.4)	3 (9.7)	1 (3.2)	–	1 (12.5)	–
12–1.59 p.m.	12 (2)	1 (3.2)	1 (3.2)	–	4 (50)	1 (12.5)
2–3.59 p.m.	–	–	2 (6.5)	–	–	–
4–5.59 p.m.	4 (0.7)	–	3 (9.7)	–	1 (12.5)	1 (12.5)
6–8.59 p.m.	16 (2.7)	1 (3.2)	14 (45.2)	–	–	5 (62.5)
9–11.59 p.m.	21 (3.5)	–	9 (29)	–	–	–

although many people take GCs in the morning, there is still variation within this. The evidence suggests this could be important in terms of the effectiveness of GCs and the side effects people may experience and may provide an opportunity to improve outcomes.

Funding: This work was supported by the Arthritis Research UK Centre for Epidemiology (20380).

Disclosure statement: The authors have declared no conflicts of interest.

**Ruth Costello¹, Rikesh Patel¹,
Jennifer Humphreys¹, John McBeth¹ and
William G. Dixon^{1,2,3}**

¹Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, School of Biological Sciences, ²Health eResearch Centre, Manchester Academic Health Science Centre, University of Manchester and ³NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Revised version accepted 14 October 2016

Correspondence to: William G. Dixon, Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, School of Biological Sciences, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK.

E-mail: will.dixon@manchester.ac.uk

References

- De Silva M, Binder A, Hazleman BL. The timing of prednisolone dosage and its effect on morning stiffness in rheumatoid arthritis. *Ann Rheum Dis* 1984;43:790–3.
- Gorter SL, Bijlsma JW, Cutolo M *et al*. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:1010–4.
- Arvidson NG, Gudbjornsson B, Larsson A, Hallgren R. The timing of glucocorticoid administration in rheumatoid arthritis. *Ann Rheum Dis* 1997;56:27–31.
- Buttgereit F, Doering G, Schaeffler A *et al*. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. *Lancet* 2008;371:205–14.
- Buttgereit F, Mehta D, Kirwan J *et al*. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). *Ann Rheum Dis* 2013;72:204–10.
- Lamia KA, Papp SJ, Yu RT *et al*. Cryptochromes mediate rhythmic repression of the glucocorticoid receptor. *Nature* 2011;480:552–6.
- Spies CM, Straub RH, Cutolo M, Buttgereit F. Circadian rhythms in rheumatology—a glucocorticoid perspective. *Arthritis Res Ther* 2014;16:S3.

Rheumatology 2017;56:495–497
doi:10.1093/rheumatology/kew398
Advance Access publication 12 December 2016

CCR5Δ32 and the genetic susceptibility to rheumatoid arthritis in admixed populations: a multicentre study

Rheumatology key message

- CCR5Δ32 is associated with protection to rheumatoid arthritis in Brazilian populations.

SIR, RA is a systemic autoimmune disease characterized by chronic and symmetric joint inflammation, which leads to bone erosion and swollen articulations caused by leucocyte infiltration, resulting in progressive loss of function. Although the triggers for the disease remain elusive, it is established that it possesses strong genetic and immunological components.

The C-C chemokine receptor type five (CCR5) belongs to a superfamily of G protein-coupled receptors with seven transmembrane domains. Several studies have suggested its role on leucocyte migration to inflammatory sites, activated by ligand binding [1, 2]. A 32 bp deletion polymorphism in the *CCR5* gene (*CCR5Δ32*) creates a premature stop codon and thus a truncated protein that is not expressed at the cell surface. Most previous studies that have assessed the influence of the CCR5 genotype in the genetic susceptibility to RA were mainly single centre studies regarding European or European-derived populations. Here, we conducted a multicentre analysis encompassing four Brazilian admixed populations from different regions of Brazil. A total of 740 patients with RA, diagnosed according to the ACR, and 676 controls from the cities of Porto Alegre (South), Belém (North), Recife (Northeast) and Ribeirão Preto (Southeast) were PCR genotyped for the *CCR5Δ32* polymorphism as previously described [3]. This study was approved by the Ethics Committees from all medical centres involved and all patients and controls gave their informed consent.

In three out of the four cities analysed, we observed a lower frequency of *CCR5Δ32* carriers in patients as compared with controls (Table 1). Remarkably, the two largest cohorts—Porto Alegre and Belém—presented significant differences in *CCR5Δ32* carrier frequencies between patients and controls ($P=0.016$ and 0.022 , respectively) despite significant differences in their ethnic composition [4]. Of note, the sample from Porto Alegre was composed exclusively of subjects of European ancestry (self-declared as white), while the other three cohorts were composed of individuals from the general population selected regardless of skin colour. Porto Alegre presented a much higher Δ32 allele frequency in both patients and controls (and was also the only population to present Δ32 homozygotes—two, both in the control group), probably due to the high admixture component of the other three cohorts (remembering that Native-American and African populations lack this allele) [4–6]. Ribeirão Preto, the only city that did not