CIRCADIAN RHYTHMS AND INFLAMMATION: GLUCOCORTICOIDS AND CHRONOTHERAPY OF RHEUMATOID ARTHRITIS

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Crucial clinical signs and symptoms of rheumatoid arthritis (RA) vary within a day and between days, and the morning joint stiffness observed in almost all patients with active RA is also considered one of the most peculiar diagnostic criteria of the disease (1) (Figure 1).

Similarly, other RA symptoms, such as joint pain and functional disability are commonly most severe in the early morning by following 24-h cycles, and are consequence of altered neuroendocrine and immune/inflammatory activities (2). Indeed, cytokines, such as tumor necrosis factor (TNF) alpha and interleukin (IL)-6, are highly increased in patients with active RA in the very late night, whereas are present at very low levels after noon (3).

Following several signalations it is growing the concept that circadian rhythms play an important role in RA symptomatology. Proinflammatory night hormones, such as melatonin (and prolactin), that follow a 24-hour daily cycle, as well as full availability of body bioenergies during the night, are recognized among the triggers/enhancers for increased release and serum concentrations of cytokines (3) (Figure 1).

On the other hands, inflammation-associated downregulation of the HPA axis activity in chronic inflammation such as in RA, is related both to increased circulating cytokines that can harm the HPA axis on all levels (hypothalamus, pituitary gland and adrenal gland) and to a consequential partial adrenal insufficiency/reduced availability of cortisol (3).

As consequence, exogenous glucocorticoid treatment is today recommended at low doses in RA since may act like a "replacement therapy" in presence of decreased endogenous cortisol (4).

The more specific items of the European (EULAR) and American (ACR) recommendations for the management of RA relate to starting disease-modifying antirheumatic drug (DMARD) therapy in early disease using a conventional DMARD strategy in combination with low doses glucocorticoids (5).

As established that pain, stiffness and functional disability show maximum level in the early morning hours, it is now clear that preventing the nocturnal rise of pro-inflammatory cytokines by glucocorticoids is more effective than treating established symptoms in the morning. The first reliable clinical study showing the superiority of night versus morning administration of glucocorticoids in RA was published in 1964 (6)..

More recently, the most advanced approach for the low-dose prednisone chronotherapy in RA included the modified-release prednisone, a timing drug release with administration at 10-11 pm and releasing prednisone around 2-3 am (7).

The effects of longterm low-dose chronotherapy with modified-release prednisone on the HPA axis have been carefully investigated in RA patients (8). The increase of cortisol plasma concentrations after injection of corticotropin-releasing hormone (CRH) was 5.5 (SD 4.37) μg/dl on regular-morning prednisone at baseline and 5.3 (4.07) μg/dl on modified-release prednisone at 12 months.

In addition, respect of the HPA with night modified-release prednisone when witching from morning to nighttime-release prednisone did not altered adrenocortical function, nor did longterm treatment of up to 12 months with modified-release prednisone compared to morning administration. As expected, nighttime-release prednisone reduced IL-6 levels in a more significant manner versus morning-release prednisone ($p< 0.01$).

Evidence based study shoved that the switch to modified-release prednisone in RA patients treated with standard glucocorticoids is advantageous both as efficacy and safety (9).

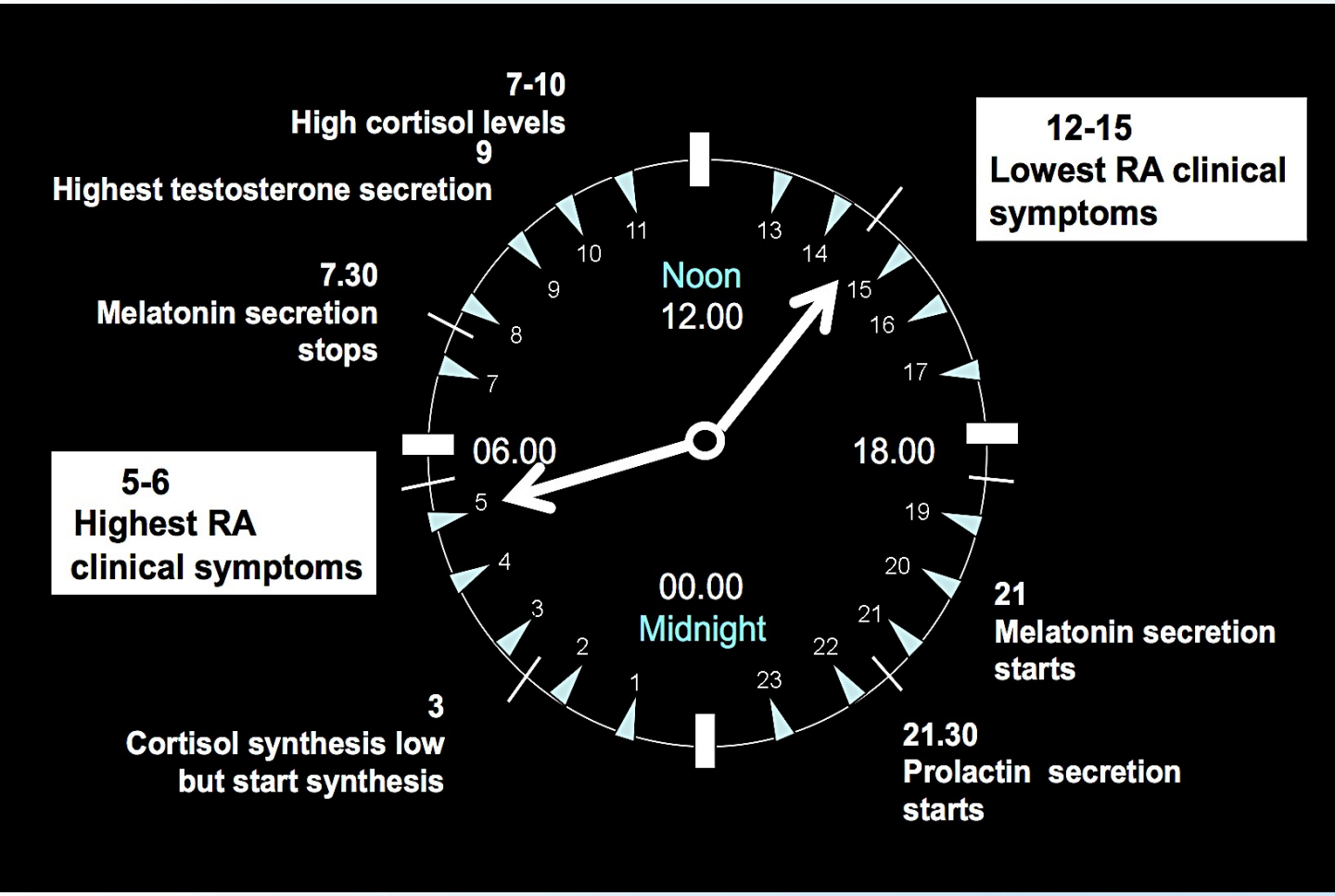
Interestingly, a recent study showed that in RA some immune cell populations (ie monocytes) lose their normal circadian rhythms, and others establish new `inflammatory` circadian rhythms (10). Therefore, since different cells involved in the inflammatory process are particularly activated during the night, other therapeutical approaches used in RA, for example with DMARDs and non steroidal antiinflammatory drugs (NSAIDs) should follow the same concepts of glucocorticoid chronotherapy.

In conclusion, the prevention/treatment of the up-regulation of immune cell activity (and related flare of cytokine synthesis) in chronic inflaamatory condition like RA, has been shown more effective when exogenous glucocorticoid availability is obtained at night-time. The positive results obtained in RA with modified-release prednisone low dose chronotherapy, following the chronobiology of the disease, seem applicable in RA even for other agents such as conventional DMARDs and NSAIDs.

Very recently the efficacy of modified-release prednisone compared to morning administration was confirmed with significant superioriry in polymyalgia rheumatica patients (11).

References:

1. Sierakowski S et al. Scand J Rheumatol Suppl. 2011;125:1–5 2. Straub RH, Cutolo M. Circadian rhythms in rheumatoid arthritis: implications for pathophysiology and therapeutic management. Arthritis Rheum 2007;56:399–408 3. Cutolo M. RMD Open. 2016 Mar 18;2(1):e000203 4. Gorter SL, Ann Rheum Dis 2010;69:1010-4 5. Smolen JS et al. Ann Rheum Dis. 2017 Mar 6. pii: annrheumdis-2016-210715. 6. De Andrade J et al. Ann Rheum Dis. 1964;23:158-62 7. Buttgereit F et al. Lancet 2008;371:205-14 8. Alten R et al. J Rheumatol 2010;37:2025-31 9. Cutolo M et al. Clin Exp Rheumatol 2013;31:498-505 10. Spies CM et al. Clin Exp Rheumatol 2015;33:34-43 11. Cutolo M et al. RMD Open 2017:3


7-10
High cortisol levels
9
Highest testosterone secretion
12-15
Lowest RA clinical symptoms
7.30
Melatonin secretion stops
Noon
12.00
06.00
18.00
5-6
Highest RA clinical symptoms
00.00
Midnight
21
Melatonin secretion starts
3
Cortisol synthesis low but start synthesis
21.30
Prolactin secretion starts