

## Metformin: the white knight fighting corticosteroid side-effects



Synthetic glucocorticoids belong to the WHO Model List of Essential Medicines and are extensively used worldwide for a broad spectrum of indications, including inflammatory and neoplastic diseases. They act via the glucocorticoid receptor, which—after ligand binding—translocate from the cytosol to the nucleus and influence gene transcription of hundreds of genes.<sup>1</sup> According to a nationwide Danish study,<sup>2</sup> the annual prevalence of glucocorticoid use in the whole population is 3%, remaining relatively stable from 1999 to 2014. Glucocorticoid use increases with age, reaching 7% in those aged 60–79 years and more than 10% in those 80 years or older.<sup>2</sup>

Iatrogenic Cushing's syndrome is the negative consequence of long-term exposure to exogenous glucocorticoids. Its typical phenotype includes metabolic, cardiovascular, immunological, psychiatric, and musculoskeletal changes associated with severe and disabling morbidity and increased mortality. Conventionally, a prednisolone equivalent dose of less 7.5 mg is considered safe. However, in a recent nationwide cohort study in 217 993 Swedish patients with asthma, the use of corticosteroids at a mean dose of 5.5 mg prednisolone equivalent was associated with a strong increase in osteoporotic fractures (HR 6.8, 95% CI 6.2–7.4) and a greater risk of death than in non-users adjusted for age, sex, and morbidity (1.3, 1.2–1.5).<sup>3</sup>

Endogenous Cushing's syndrome is rare, results from autonomous excess secretion of cortisol, and is lethal if left untreated. It is usually diagnosed late after a mean duration of 3 years, having often already induced irreversible metabolic, cardiovascular, and psychiatric damage.<sup>4</sup> Despite many advances in transsphenoidal microsurgery, the main form—ie, pituitary Cushing's syndrome, which represents 70% of cases—has a poor outcome with disease persistence in 20–30% and recurrence of up to 35%.<sup>5</sup>

The high prevalent use of exogenous glucocorticoids together with its established negative safety profile initiated the search for alternatives decades ago. Separating the desired anti-inflammatory and immunosuppressive effects from the unwanted metabolic effects has stimulated the search for a so-called

superglucocorticoid. Those approaches rely for example on enhanced biodistribution and target site accumulation of liposomal glucocorticoids targeting immune cells at specific sites,<sup>6</sup> or on selective glucocorticoid receptor modulation with tissue-specific agents acting as agonist or antagonists.<sup>7</sup>

In *The Lancet Diabetes and Endocrinology*, Ida Pernicova and colleagues<sup>8</sup> phase 2 trial enters a radically new avenue to minimise metabolic side-effects of glucocorticoid treatment: amelioration by antagonisation of its unwanted effects through tissue-specific pathway blockade. On the basis of previous promising data from the same group, they treated patients on a median dose of 20 mg prednisolone equivalent given for various chronic inflammatory conditions concomitantly with metformin or placebo. After 12 weeks, no significant changes in the primary outcome (ie, visceral-to-subcutaneous fat area ratio) were observed between the treatment groups; however, the metformin group had improved glycaemic control, lipid concentrations, and liver steatosis compared with the placebo group. None of the patients had switched to impaired glucose tolerance in the metformin group compared with seven (33%) of 21 in the placebo group. Patients in the metformin group had less hunger and reduced sugar craving than those in the control group. Other reported benefits included increased bone mineral density and improvements of intima-media thickness in the metformin group. Most remarkably, the frequency of pneumonia (1 vs 7 events;  $p=0.01$ ) and the overall rate of moderate-to-severe infections (2 vs 11;  $p=0.001$ ) was lower in the metformin group.

It is important that the authors included so many different surrogate parameters as secondary endpoints. The multitude of clinical, metabolic, and inflammatory markers, which improved with metformin, unravels in vivo an underlying conundrum of glucocorticoid's multisystemic side-effects. Downregulation by glucocorticoids of 5' AMP-activated protein kinase (AMPK), a ubiquitous signalling pathway with key roles in metabolism and the cardiovascular system,<sup>9</sup> might contribute to iatrogenic Cushing's syndrome. Metformin's restoration of AMPK activity is in this concept able to reverse the unwanted metabolic events.<sup>10</sup>



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The stunning efficacy of metformin on these surrogate parameters might call for immediate action: if metformin is capable of reversing the side-effects of glucocorticoids, why not prophylactically treat every patient exposed to excess glucocorticoids with this drug? Although this proposition might be a feasible and economic approach, several caveats have to be considered. First, this trial was a small study of only 40 patients who completed the protocol. For a common problem affecting millions of patients, only a phase 3 trial will be considered sufficient to change clinical practice. Second, the study's duration was short and not powered to investigate meaningful endpoints such as cardiovascular events and osteoporotic fractures. Finally, it has to be shown that metformin is not an ambiguous agent interfering with the anti-inflammatory and immunosuppressive effects of glucocorticoids. On the one hand, this effect might be far-fetched, since the study does not give direct evidence for reduced glucocorticoid efficacy: the dose of glucocorticoids remained similar in both groups and no flares of the inflammatory diseases are reported. On the other hand, the significant reduction in infection and pneumonia incidence might indicate a complex interaction with the immune system. Until further evidence is available, doctors might consider metformin

for patients at high risk for glucocorticoid side-effects on an individual basis and with compassionate use.

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**Martin Reincke**

Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ludwig Maximilian University of Munich, Munich 80336, Germany

- 1 Ramamoorthy S, Cidlowski JA. Corticosteroids: mechanisms of action in health and disease. *Rheum Dis Clin North Am* 2016; **42**: 15–31.
- 2 Laugesen K, Jørgensen JOL, Petersen I, et al. Fifteen-year nationwide trends in systemic glucocorticoid drug use in Denmark. *Eur J Endocrinol* 2019; **181**: 267–73.
- 3 Ekström M, Nwaru BI, Hasvold P, et al. Oral corticosteroid use, morbidity and mortality in asthma: a nationwide prospective cohort study in Sweden. *Allergy* 2019; **74**: 2181–90.
- 4 Rubinstein G, Osswald A, Hoster E, et al. Time to diagnosis in Cushing's syndrome: a meta-analysis based on 5367 patients. *J Clin Endocrinol Metab* 2019; published online Oct 29. DOI:10.1210/clinem/dgz136.
- 5 Kelsall A, Newell-Price J. Cushing's disease—from Minnie G to key issues in the early 21st century. *Lancet Diabetes Endocrinol* 2019; **7**: 959–64.
- 6 Ozbakir B, Crielaard BJ, Metselaar JM, et al. Liposomal corticosteroids for the treatment of inflammatory disorders and cancer. *J Control Release* 2014; **190**: 624–36.
- 7 Meijer OC, Pereira AM. Three percent annually on systemic glucocorticoids: facts, worries and perspectives. *Eur J Endocrinol* 2019; **181**: C23–28.
- 8 Pernicova I, Kelly S, Ajodha S, et al. The use of metformin to reduce metabolic complications and inflammation in patients on systemic glucocorticoid therapy: a randomised, double-blind, placebo-controlled, proof-of-concept, phase 2 trial. *Lancet Diabetes Endocrinol* 2020; published online Feb 25. [http://dx.doi.org/S2213-8587\(20\)30021-8](http://dx.doi.org/S2213-8587(20)30021-8).
- 9 Herzig S, Shaw RS. AMPK: guardian of metabolism and mitochondrial homeostasis. *Nat Rev Mol Cell Biol* 2018; **19**: 121–35.
- 10 Christ-Crain M, Kola B, Lolli F, et al. AMP-activated protein kinase mediates glucocorticoid-induced metabolic changes: a novel mechanism in Cushing's syndrome. *FASEB J* 2008; **22**: 1672–83.