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Review

Glucocorticoid administration in athletes: Performance, metabolism and detection

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ABSTRACT

It is generally acknowledged in the sporting world that glucocorticoid (GC) use enhances physical performance. This pharmacological class is therefore banned by the World Anti-Doping Agency (WADA) in in-competition samples after systemic but not local (defined as any route other than oral, intravenous, intramuscular or rectal) administration, which thus allows athletes to use GCs for therapeutic purposes. According to the 2016 WADA list, the urine reporting level for all GCs is set at 30 ng/ml to distinguish between the authorized and banned routes of administration. The actual data on the ergogenic effects of GC intake are nevertheless fairly recent, with the first study showing improved physical performance with systemic GC administration dating back only to 2007. Moreover, the studies over the last decade coupling ergogenic and metabolic investigations in humans during and after GC intake have shown discrepant results. Similarly, urine discrimination between banned and authorized GC use remains complex, but it seems likely to be improved thanks to new analytical studies and the inclusion of the authorized GC uses (local routes of administration and out-of-competition samples) in the WADA monitoring program. In this review, we first summarize the current knowledge on the ergogenic and metabolic GC effects in humans during various types of exercise. We then present the antidoping legislation and methods of analysis currently used to detect GC abuse and conclude with some practical considerations and perspectives.

Contents

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1. Introduction

Many athletes use glucocorticoids (GCs) for either therapeutic or doping purposes [1–3], although no study has yet determined the actual prevalence. The anti-inflammatory effects of this pharmacological class of drugs make them the treatment of choice for asthma and painful chronic musculoskeletal injuries [1]. GCs have also been abused for doping over the past 50 years [4], even though very few studies were conducted before the last decade to test their ergogenic effects during exercise.

Due to concerns about their doping effects, the World Anti-Doping Agency (WADA) has put certain restrictions on these drugs, and GCs are now banned in in-competition samples after systemic but not local (administration routes other than oral, intravenous, intramuscular or rectal) administration [5]. This policy allows athletes to use GCs for therapeutic purposes, and a urine reporting level has been set to distinguish between the allowed and forbidden routes of administration.

Previous reviews [6,7] have addressed the question of why GCs should remain on the WADA list, so this is not the intention of this review. Instead, we first summarize the current knowledge on the ergogenic and metabolic effects of GCs in humans during various types of exercise, drawing on the data from recent physiological and analytical studies dealing with this complex pharmacological class (i.e., various molecules, metabolites, routes, modes of administration). We then present the antidoping legislation and methods of analysis currently used to detect GC abuse, and conclude with some practical considerations and perspectives.

2. Glucocorticoids: performance and metabolism

The following sections address the potential ergogenic and metabolic effects of GCs during varying types of exercise that are categorized according to power output and time to exhaustion or to race completion.

2.1. Glucocorticoid administration and graded exercise tests

2.1.1. Performance

Two studies [8,9] found no effect of GC intake on VO_2 max (maximal oxygen consumption) or maximal power output during graded exercise protocols lasting 8–20 min. The first study [8] examined the effects of oral intake of dexamethasone at a dosage of 1 or 3 mg/day/4.5 days in healthy young men. The second study [9] examined the effects of daily inhalation of 800 μg of budesonide for 4 weeks in young well-trained male cyclists and rowers.

2.1.2. Metabolism

Neither of the studies referred to in Section 2.1.1 [8,9] reported any significant change in body weight after 4.5 days of systemic dexamethasone administration at the two dosages or 4 weeks of budesonide inhalation. However, Marquet et al. [8,10] reported several hormonal and metabolic responses to oral dexamethasone intake. This did not seem to be the case after budesonide inhalation [9], probably because of the lack of significant portion of the active compound absorbed into the circulation [11]. Therefore no systemic repercussions (i.e., alterations of hormonal, metabolic or functional responses) were observed in this study [9], but it should also be noted that fewer parameters were investigated. After 4.5 days of oral dexamethasone administration at 1 or 3 mg/day, both the basal and exercise plasma and saliva concentrations of all the investigated steroids were dramatically decreased: cortisol, androstenedione, dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S), with the exception of testosterone, and this, independently of the dose administered. Exercise plasma adrenocorticotropic hormone (ACTH), beta-endorphins, aldosterone, heart rate and blood glucose were also lowered by the GC, whereas plasma atrial natriuretic factor was increased. No change in lactate was found [8,10].

2.1.3. Synthesis

"Rumor" has it that athletes do not use GCs to increase power output, and it seems unlikely that local or systemic GC intake improves performance during this kind of exercise, despite the many metabolic changes demonstrated after systemic GC administration. However, there are too few studies to reach a strong conclusion.

2.2. Glucocorticoid administration and short-intense exercise

2.2.1. Performance

The first study in humans to directly test the ergogenic effects of GCs during short-intense exercise was conducted in 2008 in

healthy recreationally active subjects. Nordsborg et al. [12] tested the effects of 5 days of dexamethasone (4 mg/day) per os (i.e., oral route, PO) on one-legged knee-extensions at several intensities: a continuous bout at low intensity, a moderate bout with a fixed duration (5 min) followed by another moderate bout until exhaustion, and a bout at high intensity consisting of fixed-duration exercise (1 min 40 s) followed by another high-intensity bout to exhaustion. The authors reported no significant ergogenic effect at high intensity, in contrast to an effect observed at moderate intensity. However, using similar GC administration and a similar recreationally active population, the same team more recently demonstrated [13] an improvement in performance during a single one-legged kicking bout to exhaustion, without a change in the loss of muscular force generating capacity.

Lastly, in 2014 Zorgati et al. [14] examined the ergogenic effects of 7 days of 60 mg of prednisone PO in male recreational athletes during repeated bouts of high-intensity exercise consisting of hopping on the dominant leg for 30 s three times consecutively and then hopping until exhaustion, with 5-min intervals of passive recovery. The absolute peak force of the dominant leg was significantly increased by GC but only during the first 30-s hopping bout, whereas time to exhaustion was not significantly changed after GC treatment [14].

2.2.2. Metabolism

Although the ergogenic effects of GCs have been explored only very recently during short-intense exercise, the metabolic effects during this type of exercise were explored earlier by Deuster et al. [15,16] and Petrides et al. [17,18]. Petrides et al. [17] tested the metabolic repercussions of both acute hydrocortisone (100 mg) and dexamethasone (4 mg) PO in moderately trained subjects during ten repeated 30-s bouts at 90% VO_2 max with 30-s intervals of passive recovery. The authors observed no change in oxygen consumption or heart rate during the exercise after GC administration, but found significant decreases in ACTH and plasma cortisol (for dexamethasone) and a significant increase in arginine vasopressin. Interestingly, it appears that two groups of subjects could be characterized: "high" responders, with only a partial suppression of ACTH and cortisol release stimulated by exercise, and "low" responders, with the classical complete suppression of both. The two groups also showed differential hypothalamic-pituitaryadrenal (HPA) axis reactivity to psychological and physical stress and, moreover, these high and low responders had different baseline patterns of interleukin-6 (IL-6) and lymphocyte subsets, which may reflect differential sensitivity to endogenous GCs [19]. Deuster et al. [16] thus estimated that around 30% of healthy men and women are high responders. Duclos et al. [20] found about the same proportion of "high" responders in endurance-trained men but not in sedentary subjects, and interpreted this latter finding as an indication of decreased pituitary sensitivity to GCs in endurance-trained subjects. Importantly, the strength of the stimulus can dictate the magnitude of ACTH and cortisol escape as exercise at 100% of maximal capacity promoted escape in more individuals than exercise at 90% [15]. Moreover, there is clearly a dose-dependent effect [16], with total suppression of ACTH and cortisol release observed in both high and low responders with higher dosages or short-term treatment [8,10,21–23]. The relevant question now is whether these differences in reactivity of the ACTH-cortisol axis between the high and low responder groups are implicated in individual short-term function and long-term health.

As previously shown by Papanicoulos [24], Zorgati et al. [14] recently found that basal and end-exercise plasma pro-inflammatory IL-6 and saliva DHEA were decreased and anti-inflammatory interleukin-10 (IL-10) was increased by GC versus placebo intake, whereas no significant change was found in blood lactate and tumor necrosis factor-alpha (TNF-α) or saliva testosterone. This increased IL-10 release from macrophages with GCs cannot be related to the higher muscle-derived IL-6 levels but, interestingly, it should be noted that the anti-inflammatory effects of GC appeared maximal and stable from the beginning of treatment, both in rest and exercise conditions, whereas hormonal concentrations continued to decline during 1 week of treatment with 60 mg/day prednisone [25].

Regarding the effects on muscle, Nordsborg et al. [12,26] reported that GC increased maximal Na^+K^+ pump activity in both vastus lateralis and deltoid muscles, with a decrease in femoral venous potassium concentration at all exercise intensities. Thigh potassium release during one-legged knee-extension exercise was lower with GC at low and moderate intensity but not at high intensity. The authors concluded that an increased Na^+K^+ pump expression per se is of importance for thigh K^+ reuptake at the onset of low and moderate intensity exercise, but less important for high intensity exercise. More recently, Casuso et al. [13] reported classical electromyography (EMG) increases during single one-legged kicking exercise with GC and placebo but similar EMG root means, which invalidates the hypothesis of a change in fatigue level caused by GC originating from the central nervous system during this type of exercise. Last, the ergogenic effects of GCs may be mediated by direct induction of the metabolic transcription factor KLF15, defining a downstream pathway distinct from that resulting in GC-related muscle atrophy and improving lipid and amino acid metabolism [27].

2.2.3. Synthesis

At this time, it is not clear whether GCs actually improve performance during short-intense exercise. Although GC ergogenic effects appear blunted with repeated exercise and with muscle fatigue, the effects may occur during a single bout of high-intensity exercise, which is required in most individual intense sports events. When this potentially ergogenic effect does occur, it is probably due to a local muscular effect, without direct link to the anti-inflammatory response.

2.3. Glucocorticoid administration and endurance exercise

2.3.1. Performance

Randomized cross-over studies have carefully examined the performance, hormonal and metabolic responses to GCs in recreationally trained male and female athletes.

The first study [21] tested the effects of a therapeutic dose of oral corticosteroid (20 mg of prednisolone) alone or associated with a beta-2 agonist on performance and substrate response during intense submaximal exercise, i.e., 80–85% VO_2 max, until exhaustion in healthy moderately trained male volunteers. Performance did not change with GC intake and the authors suggested that the relatively short duration of the exercise (about 20 min) may have explained the lack of improved performance. Therefore, the researchers [28] tested the same GC administration versus placebo in male recreational athletes during a less intensive trial, i.e., 70–75% VO_2 max, conducted to exhaustion in about 50 min. As in the previous study, no improvement was observed despite the longer exercise duration. The same team [22] then investigated the impact of short-term GC intake (60 mg of prednisolone/day/7 days) in a similar population and with the same exercise intensity (70–75% VO_2 max) and this time found a marked improvement in performance, which was also observed after short-term GC intake (50 mg of prednisone/day/7 days) in recreationally trained females [29]. An improvement in performance therefore seems to be irrespective of sex, but the magnitude of improvement may be positively related to the fitness status of the subjects and/or the type of physical exercise. Indeed, in view

of the legal risks of administering doping substances to elite athletes and in order to determine whether the above-cited results could be extrapolated to elite athletes [11], Collomp et al. [23] investigated the effects of short-term prednisolone ingestion (60 mg/day/7 days) combined with intense training, which consisted of standardized physical training 2 h/day, on exercise performance. With this training-GC combination, the authors reported an average increase in cycling time until exhaustion of about 80% compared with the average increase of 54% obtained without training, with the greatest increases in time to exhaustion with prednisolone obtained in those subjects having the best trial times with placebo [23]. Last, Hostrup et al. [30] very recently tested the effects of 2 weeks of budesonide inhalation (1.6 mg/day) in healthy trained male subjects and reported no change in cycling to fatigue at 90% of incremental peak power output in response to a 4 mg terbutaline inhalation.

2.3.2. Metabolism

Acute oral prednisolone administration was found to increase lipid oxidation and decrease carbohydrate oxidation during a 60-min submaximal exercise (60% VO_2 max), with an increase in total energy expenditure during exercise [31], possibly resulting from an accelerated lipolysis, ketogenesis and proteolysis [32]. However, the exact mechanisms have not yet been elucidated. The involvement of the increased activity of the ATP-dependent Na^+K^+ pump in the change in GC energy expenditure cannot be ruled out, even though it appears likely that the hormonal alterations induced by GCs are implicated.

Basal and exercise ACTH, DHEA and IL-6 concentrations were significantly decreased in experiments conducted at submaximal exercise with acute GC intake versus placebo [21], whereas no variation was found in growth hormone (GH), insulin, blood glucose or lactate. The metabolic changes during submaximal exercise after short-term GC administration (50–60 mg prednisone or prednisolone/day/7 days) appeared to be much more marked, irrespective of sex. Similar to findings for acute administration, decreases in ACTH, DHEA and IL-6 were observed [22,23,29], but the hormonal alterations induced by short-term GC administration were no longer restricted to the HPA axis. Indeed, Arlettaz et al. [22] showed significant decreases in prolactin (PRL), GH and testosterone during a submaximal exercise at 70–75% VO_2 max in male recreationally trained subjects. The metabolic and functional consequences of an exercise-induced decrease in DHEA, testosterone or GH with short-term GC administration remain to be elucidated. However, muscle-derived IL-6, which is released in high amounts into the circulation during exercise, depending on intensity and duration, is likely to exert an effect on the liver and adipose tissue, thereby contributing to the maintenance of glucose homeostasis during exercise and mediating exercise-induced lipolysis [33]. Moreover, low muscle glycogen content stimulates IL-6 production. It may therefore be suggested that IL-6 inhibition by GC intake may be linked directly or indirectly to the decrease in carbohydrate oxidation after GC treatment [31,33].

Prolactin reflects alterations in both central brain 5-hydroxytryptamine (serotonin) and dopaminergic activity. Therefore, the decrease in PRL may have delayed the onset of "central fatigue" and thereby contributed to the significant improvement in performance found [22]. In parallel, the authors observed higher exercise blood glucose, insulin, and lactate with GC intake, although the changes in these parameters have not been systematic. For example, in another study, exercise insulin and lactate were not increased by GC in male subjects when GC and physical training were combined [23]. Moreover, blood glucose and insulin levels did not increase during submaximal exercise at 70–75% VO_2 max in females [29], suggesting that women may be less sensitive than men to GC-induced insulin resistance. In healthy women performing a longer moderate submaximal exercise (60% VO_2 max for 2 h) [34], the classical hormonal alterations induced by GC were coupled with increases in plasma branched-chain amino acids and other essential amino acids from 60 min to the end of exercise, whereas blood glucose was significantly higher from 90 min to the end of exercise. The link between GCs and proteolysis has been well established at rest [35], but further studies are necessary to assess whether GC intake induces an increase in proteolysis and/or gluconeogenesis during exercise and, if so, how this increase directly contributes to performance during long-lasting endurance exercise [34].

Lastly, in both male and female subjects [36,37], basal leptin and adiponectin were significantly increased by 7 days of prednisolone administration, with no change in food intake, body weight or composition and irrespective of sex. However, it cannot be ruled out that the higher level of leptinemia might have been the preliminary sign of a future increase in fat mass [37] if GC treatment had been prolonged.

2.3.3. Synthesis

The ergogenic effects of short-term systemic GCs during endurance exercise have now been clearly demonstrated in recreationally trained athletes irrespective of sex, with a possible potentiation of GC ergogenic effects when combined with physical training. However, the complexity of the central and peripheral responses makes dissociation of the possible causal effects on performance difficult to distinguish at this time. Even though at first view an "impregnation" with GC seems necessary to improve performance, new studies with higher doses are needed to clarify the potential ergogenic effects of acute systemic GC administration.

2.4. Glucocorticoid administration and field studies

2.4.1. Performance

To our knowledge, only one field study has been conducted to test the ergogenic effects of GCs. Casuso et al. [13] explored performance in young healthy nonsmoking subjects during a 20-m shuttle run (yo-yo test) and a 30-m sprint test after 5 days of 4 mg of dexamethasone intake. The authors reported improvement in performance during the 20-m shuttle run with very high inter-subject variation (19 ± 23%), but no improvement during the 30-m sprint test.

2.4.2. Metabolism

Unfortunately, no metabolic parameters were investigated in the study referred in Section 2.4.1.

2.4.3. Synthesis

New field studies that include both ergogenic and metabolic parameters are needed, using tests adapted to the population being investigated.

2.5. Post-Glucocorticoid administration effects

2.5.1. Performance

No study to our knowledge has investigated performance in the days or weeks following GC treatment either in the laboratory or in the field.

2.5.2. Metabolism

Prolonged suppression of HPA function has been widely demonstrated in patients after chronic GC therapy, with many side effects [38,39]. However, it is assumed that athletes limit GC use, whether for therapeutic or doping purposes, to only a few days in order to avoid the well-known muscle catabolic effects. We have therefore

limited this review to studies investigating metabolism after short-term treatments.

Inhaled GC, alone or combined with long-acting beta-2 agonists, is now the first-line medication for asthma. It is generally assumed that the systemic pathway of GCs remains low for this local administration route [40–42], with a slight decrease in plasma cortisol concentration but without significant HPA axis inhibition for short-term utilization.

Although intra- or periarticular administration of GC is local, a significant portion of the active compound might be absorbed into the circulation [43]. Suppression of the HPA axis with secondary adrenal insufficiency seems to be dependent on many factors, including the type and amount of the injected steroid, the type of the injected depot preparation, the joint, and the number of joints injected simultaneously. Indeed, Gless et al. [44] reported that the suppressant effect of betamethasone (Celestan Depot®, MSD, Frankfurt, Germany, i.e., betamethasone sodium phosphate and acetate) on the adrenal cortex after intraarticular (IA) injection is similar to the effect of intramuscular (IM) application, with a return to the normal range after 4 days. Similarly, Habib et al. [45] observed no adrenal insufficiency in elderly patients after IA injection in the knee with 1 ml of Celestone Chronodose®, MSD, Bruxelles, Belgium, i.e., betamethasone sodium phosphate and acetate). However, the same team [46] reported a transient high rate of secondary adrenal insufficiency after IA injection in the knee with Diprospan®, MSD, Petah-Tikva, Israel, which is composed of a similar immediate-release component, betamethasone sodium phosphate, and a sustained-release component, betamethasone dipropionate. Using a single IA methylprednisolone injection between 20 and 160 mg, Mader et al. [47] tested the basal cortisol level and response to ACTH stimulation and showed recovery in most patients with rheumatic disease after 1–2 weeks, with the magnitude of the suppression depending on the injected dose and the inflammatory joint disease. To our knowledge, only Duclos et al. [48] have conducted a study in trained athletes. These authors reported that a single IA injection of cortivazol (sustained-release) or betamethasone (combination of immediate- and sustained-release) for post-traumatic or micro-traumatic skeletal injuries in healthy young male athletes lowered cortisol levels for up to 14 days following the end of treatment compared with pre-injection levels.

Regarding oral systemic intake, Streck et al. [49] compared cortisol responses to insulin-induced hypoglycemia and synthetic ACTH in normal men before and after GC treatment (50 mg prednisone/day/5 days). The authors reported a significant decrease in peak cortisol response after both tests 2 days after prednisone therapy, with a return to pretreatment test values 5 days after the end of treatment. Carella et al. [50] evaluated HPA function, with and without stimulation, in normal adults before and after a short burst of prednisone (120 mg/day/3 days, then tapering over the next 4 days) and concluded that HPA function was normal 1 week after prednisone discontinuation. Watson et al. [51] performed corticotrophin-releasing hormone (CRH) tests in adult volunteers before and after a 2-week course of prednisolone (50 mg/day) and demonstrated that 48 h after the end of treatment, the recovery of ACTH secretion was complete but the cortisol response to CRH was still depressed. Similarly, Brigell et al. [52] tested the responses to CRH before and after administration of 50 mg prednisolone/day/2 weeks in normal male volunteers. The cortisol levels, both basal and in response to CRH, were significantly suppressed 24 h post-prednisolone and returned to pretreatment levels by 72 h post-prednisolone. Last, Spiegel et al. [53] evaluated adrenal function, with and without stimulation, in cancer patients receiving chemotherapy that included GC (50 mg prednisone/day/5 days), and demonstrated that 13 of 14 patients had suppressed adrenal function for at least 24 h, with almost all patients returning to normal function between posttreatment days 2 and 4. To our knowledge, only two studies have been conducted in healthy subjects with regular sports practice, after treatment with 50–60 mg/day/7 days of prednisone [54,55]. These two studies confirmed the findings of those conducted in patients, with a return to basal values of both DHEA and cortisol concentrations 48–72 h after the end of GC treatment. Moreover, this treatment induced a complete disappearance of the DHEA diurnal pattern, which lasted 2 days posttreatment [55].

2.5.3. Synthesis

The return to basal values after GC seems to depend mostly on the molecule used and the administration route. It appears that 2–3 days is enough for the return to basal hormonal values after oral short-term administration of intermediate-acting GCs, but more and less time would probably be necessary for, respectively, long-acting (betamethasone/dexamethasone) and short-acting (hydrocortisone) GCs. New studies are also needed to ascertain the time-course for the return to basal values for ergogenic and other metabolic parameters.

With local intra- and periarticular GC administration, the GC repercussions are more prolonged, in particular for sustained-release long-acting GCs. Given the risks of biological adrenal suppression, therapeutic intra- or periarticular administration of GCs, even though allowed by WADA, should remain exceptional and seems inconsistent with sports training.

3. Glucocorticoids: kinetics and detection

3.1. GC pharmacokinetics

The equivalent doses and the plasma and biological half-lives of the most frequently used GCs are presented in Table 1, along with their maximal therapeutic systemic and local doses wherever available [42]. Topical doses are not presented. Several studies have investigated the pharmacokinetics of these GCs and the various administration routes, but very few have investigated urine concentrations. We present here only the latter, all obtained in individuals not undergoing physical exercise.

3.1.1. Intermediate-acting glucocorticoids

About 10–20% of the prednisolone molecule and about 5–10% of the prednisone molecule were found in urine, after either PO or intravenous (IV) therapeutic use [56–60]. In both cases, the percentage was dose-dependent. The percentage for methylprednisolone after PO intake appeared to be a little lower (between 3 and 7%), whereas percutaneous absorption was less than 1% [61–63]. Regarding triamcinolone acetonide, only about 1% of the administration was found as parent drug after either PO or IV administration [64,65].

3.1.2. Long-acting glucocorticoids

Petersen et al. [66] found about 5% of the parent drug in urine after a single betamethasone IV intake, and Rose et al. [48] found about the same elimination after IV dexamethasone administration.

3.2. WADA legislation

According to the 2016 WADA list, local administration of GCs is allowed both in- and out-of-competition, but systemic administration of GCs is prohibited in in-competition urine samples, as mentioned in the S9 “Glucocorticoid class” [5]. Therefore, as stated by the U.S. anti-Doping Agency (USADA) on its “Athlete Guide to the 2015 Prohibited List” website:

Table 1
Glucocorticoid (GC) conversion table/half-life/maximal therapeutic dose.

GC (INN)	Equivalent dose (mg)	Plasma half-life (hr)	Biological half-life (hr)	Maximal therapeutic systemic dose (PO, IM, IV)	Maximal therapeutic local dose (IA, Inh)
Short-acting					
Cortisone	25	1.3–2.0	8–12	500 mg	
Hydrocortisone	20	0.5–1.5	8–12	500 mg	
Intermediate-acting					
Deflazacort	6	1.1–1.9	18–36	90 mg	
Methylprednisolone	4	1.5–3.0	18–36	1 g/day	80 mg (IA)
Prednisolone	5	2.0–3.5	18–36	0.35–2.0 mg/kg/day	
Prednisone	5	1.0–3.5	18–36	0.35–2.0 mg/kg/day	
Triamcinolone Acetonide	4	4.5–5.5	18–36	80 mg	80 mg (IA) 1600 μg/day (Inh)
Long-acting					
Betamethasone sodium phosphate/acetate	0.75	2.5–4.5	36–54	0.05–0.2 mg/kg/day	
Cortivazol		>5	>60		1.25–3.75 mg/kg/day (IA)
Dexamethasone	0.75	2.5–4.5	36–54	40 mg/day/4 days	
Inhaled GC (often coupled with long-acting beta2-agonists)					
Beclomethasone		2.5–3.0			2000 μg/day (Inh)
Budesonide		2.5–3.0		12 mg (mainly local effect)	1600 μg/day (Inh)
Fluticazone		2.5–3.0			2000 μg/day (Inh)

INN: international nonproprietary names for pharmaceutical substances; PO: per os; IM: intramuscular; IV: intravenous; IA: intraarticular; Inh: inhalation.

- Athletes who are prescribed oral, rectal, IV or IM glucocorticoids may take these medications out-of-competition without submitting a TUE (therapeutic use exemption), as long as the prohibited substance has cleared their system prior to the time defined as "in-competition". If athletes need to use these routes shortly before or during competition, they must obtain a TUE.
- The time it takes for glucocorticoids to clear from the athlete's body depends on many variables and cannot be predicted by USADA. This is up to the athletes, their doctor, and their pharmacist to determine.
- Injections of glucocorticoids around tendons, into joints, and epidurals (into the spine) are permitted, but an injection into a muscle is prohibited.
- Inhalation of glucocorticoids (e.g. for asthma) is permitted.
- Topical use of glucocorticoids (e.g., anti-rash cream, hemorrhoidal creams used on the surface, etc.) is [sic] permitted. Be aware, however, that some hemorrhoidal suppositories or rectal creams contain glucocorticoids and are prohibited in-competition.

GCs were recently added to the monitoring program, which was established by WADA according to the World anti-Doping Code (Article 4.5) regarding substances "*which are not on the Prohibited List, but which WADA wishes to monitor in order to detect patterns of misuse in sport.*" Thus, GCs have been part of the monitoring program for out-of-competition samples (all routes of administration) since 2012, and for in-competition samples (by routes of administration other than oral, intravenous, intramuscular or rectal) since 2015. GCs are not considered threshold substances, i.e., with strict decision limits for the confirmatory quantification. They are therefore only relevant of the Minimum Required Performance Levels (MPRL) values set at 30 ng/ml.

3.3. Current detection

3.3.1. Screening/confirmation testing procedure

Contrary to androgenic anabolic steroid detection, WADA does not require one reference method for both the initial detection test (i.e., screening) and the confirmation test for GCs. Two techniques with good selectivity and sensitivity are currently used in antidoping laboratories for the screening and confirmation procedure: liquid chromatography (LC) and gas chromatography (GC) coupled with mass spectrometry (MS), most often in tandem (LC-MS/MS and GC–MS/MS). Before the introduction of LC-MS/MS, GCs were mainly detected by GC–MS, but a time-consuming derivatization step was necessary because of the low volatility of most corticosteroids. LC-MS/MS thus appears to be the best choice for GC analysis [67–72] as the extracts can be directly injected into the LC system.

Sample preparation for the analysis of GCs in the urinary matrix nevertheless requires several clean-up steps, even with LC-MS/MS. The most widely used protocol consists of solid phase extraction prior to or after the hydrolysis step with β-glucuronidase from *Escherichia Coli*, but protocols without enzymatic hydrolysis have also been proposed in the literature [73]. Current GC detection is based on measurement of the parent drug, except for budesonide. Indeed, the only GC metabolite required by the WADA technical document (TD2015MPRL) is 6β-hydroxy-budesonide, which is mandatory for the detection of budesonide administration by systemic routes.

3.3.2. Particular case: false detection of prednisolone use

Recently, the presence of endogenous prednisolone in human urine has been reported [74], potentially through the microbial transformation of cortisol to prednisolone (<1%). To date, no isotope-ratio mass spectrometry (IRMS) method has been developed to overcome this problem but, given that an adverse analytical finding is considered to be a concentration above 30 ng/ml, no false positive would result from such a microbial transformation.

3.3.3. WADA statistical report

Table 2 presents the frequency of GCs detected by WADA over the last few years. It is important to recall that the detection concerned only the in-competition samples.

Budesonide was the most frequently detected GC, with a decrease in the number of cases since the modification of the technical document in 2014 and the determination of another metabolite, 6β-hydroxy-budesonide, for detecting systemic budesonide administration. It should be noted that budesonide, even when taken orally, mainly has a local effect, with 80–90% absorbed by the ileum and colon, and very low bioavailability [41,75,76].

Prednisone and prednisolone were also detected with high frequency, making up more than 30% of the detected cases in the last 3 years. Because of the interconversion of prednisone (prodrug)

Table 2
Frequency of glucocorticoids (GC) detected by WADA from 2010 to 2014.

GC	2010	2011	2012	2013	2014
Betamethasone	27	25	30	35	34
Budesonide	111	113	157	135	74
Deflazacort	3	1			1
Dexamethasone	8	21	18	18	12
Fluticazone	1	2	1	2	
Methylprednisone	7	16	15	14	14
Prednisone	16	19	60	55	44
Prednisolone	9	19	67	58	56
Prednisone + prednisolone	39	40			
Triamcinolone	6	2	1	1	1
Triamcinolone acetonide	7	16	16	12	16
Total GC	**234**	**274**	**365**	**330**	**252**
% GC/total infraction	**4.2**	**4.9**	**8.1**	**6.3**	**8.0**

GC: glucocorticoid; WADA: World Anti-Doping Agency.

Table 3
Synthesis of studies exploring glucocorticoid (GC) ergogenic effects on performance in athletes.

Protocol	GC	Route of administration (PO, Inh)	Mode of administration (A, ST)	Dose (and environmental factors)	Athletes (HT, RT, Sed)	Sex (M, F)	Performance	First Author	Years
Graded exercise									
VO_2 max	Dexamethasone	PO	ST	1–3 mg/day/4.5 days	RT, Sed	M	=	Marquet	1999
VO_2 max	Budesonide	Inh	ST	800 μg/day/4 weeks	HT	M	=	Kuipers	2008
Short-intense exercise									
One-legged knee-extensions at several intensities (I)	Dexamethasone	PO	ST	4 mg/day/5 days	RT	M	High I: = Low I: +	Nordsborg	2008
One-legged kicking bout to exhaustion	Dexamethasone	PO	ST	4 mg/day/5 days	Sed	M	+	Casuso	2014
Hopping 30 s, 3 times, and till to exhaustion	Prednisone	PO	ST	60 mg/day/7 days	RT	M	Time to exhaustion: = Peak force: +	Zorgati	2014
Field study									
20-m shuttle run (yo-yo) 30-m sprint test	Dexamethasone	PO	ST	4 mg/day/5 days	Sed	M	Yo-yo: + 30-m sprint: =	Casuso	2014
Endurance exercise									
80–85% VO_2 max cycling until exhaustion	Prednisolone	PO	A	20 mg	RT	M	=	Arlettaz	2006
70–75% VO_2 max cycling until exhaustion	Prednisolone	PO	ST	60 mg/day/7 days	RT	M	+	Arlettaz	2007
70–75% VO_2 max cycling until exhaustion	Prednisolone	PO	A	20 mg	RT	M	=	Arlettaz	2008
70–75% VO_2 max cycling until exhaustion	Prednisolone	PO	ST	60 mg/day/7 days with 2 h training/day	RT	M	+	Collomp	2008
70–75% VO_2 max cycling until exhaustion	Prednisone	PO	ST	50 mg/day/7 days	RT	F	+	Le Panse	2009
90% peak power output cycling until exhaustion	Budesonide	Inh	ST	1.6 mg/day/2 weeks in response to terbutaline	HT	M	=	Horstrup	2016

Legend: GC: glucocorticoid; PO: per os; Inh: inhalation; A: acute; ST: short-term; HT: highly trained; RT: recreationally trained; Sed: sedentary; M: male; F: female.
+: performance improvement; =: no change in performance.

and prednisolone (active molecule), urine often contains both. Since 2012, no distinction has been made in the statistical reports of detection of prednisone and prednisolone alone or combined. No case of exogenous hydrocortisone (i.e., cortisol) has been detected at this time and it appears very difficult to set a cortisol threshold because of the circadian rhythm and the very high variation induced by physical exercise [77].

4. Practical considerations and perspectives

4.1. Mechanisms for improved performance?

The ergogenic effects of short-term systemic GC intake today seem indisputable for endurance but not for short-intense exercise as shown in Table 3. Therefore, the risk of GC abuse in aerobic sports/disciplines might be feared, but this can easily be checked via the WADA statistics.

It has generally been assumed that GC improves endurance performance through its neuro-stimulatory, anti-inflammatory and metabolic effects, which have been well described at rest [1,2]. The numerous alterations in hormonal parameters that occur during endurance exercise (i.e., decreases in ACTH, DHEA, GH, and PRL) indicate that short-term systemic GC treatment induces both central and peripheral effects, not limited to the HPA axis.

Further study is needed to assess whether a change in substrate mobilization is a mechanism by which GC administration enhances endurance during long-lasting exercise. Similarly, although GC-induced anti-inflammatory responses and mood states do not seem to be linked to improved performances [9,78], further studies

are needed to assess whether GC intake delays the onset of "central fatigue" [22] and to determine the impact of GCs on human motor drive and voluntary muscular activation during both endurance and short-intense exercise [13]. Last, new studies are needed to investigate exercise performance and metabolism during the weeks following short-term treatment.

4.2. GC as threshold substances?

There is broad agreement that systemic GC use should be included in the list of substances and methods prohibited in-competition. In view of the ergogenic effects of short-term systemic GC intake, it appears essential to at least keep GCs in the out-of-competition monitoring program.

Corticosteroids are not considered threshold substances at this time, with a single reporting level of 30 ng/ml that applies to all GCs. The question now is whether to set a specific threshold for each GC. A first response seems to be found in the 2015 decision to include GCs administered by routes other than oral, intravenous, intramuscular or rectal use in the WADA monitoring program for in-competition samples. Moreover, recent studies [67–72] have evaluated the urine profiles of several GCs (betamethasone, budesonide, methylprednisolone, prednisolone, triamcinolone acetonide) and their metabolites to refine the 30 ng/ml reporting level for distinguishing between the allowed and forbidden pathways. It appears that a lower concentration of either 6 beta-hydroxy-budesonide [68] or triamcinolone acetonide [72] may help to better discriminate between local and systemic routes. The same team also reported that adding specific metabolites would significantly increase the detection time after GC administration, as these metabolites can be found in urine up to 2–6 days after administration, even though the parent substance usually disappears within the first 24 h [69,70]. The problem nevertheless remains complicated. First, one must take into account the inter-individual variations in GC metabolism, with, moreover, the possible interaction of altitude exposure [79] and oral contraceptive use [80], but not smoking [58]; second, the interaction of anaerobic and aerobic exercise on GC pharmacokinetics remains largely unknown [81]; and third, a change in legislation for the currently allowed intra-and periarticular administration may be considered as urine samples cannot be used to distinguish between this authorized and the banned routes.

Regarding natural corticosteroids such as hydrocortisone and cortisone, proof of exogenous administration is even more complicated. As previously mentioned in Section 3.3.3, a urine cortisol threshold would not be efficient, in view of the large variation in cortisol secretion induced by physical exercise [77]. Several approaches have therefore been proposed to distinguish endogenous secretion from exogenous use. For example, Meklat et al. [82] studied the usefulness of the urine ratio of tetrahydrocortisol (THF) to tetrahydrodeoxycortisol (THS). In parallel, Buisson et al. [83] and Brooker et al. [84] described an analytical protocol for unambiguously establishing the endogenous or exogenous origin of the major and minor metabolites of hydrocortisone and cortisone. As for the endogenous anabolic androgenic steroids, the methodology proposed here is based on IRMS analysis, which provides the carbon isotope ratio (CIR) $^{13}C/^{12}C$ of the targeted corticosteroids.

4.3. Inclusion of an indirect detection with urine/blood/saliva analysis in the Athlete Biological Passport?

As noted in Section 4.2, direct detection of GC use in urine is currently time-limited after local or systemic administration, with the exception of intra- and periarticular administration. Therefore, indirect markers of GC administration have been proposed. For example, Guinot et al. [85] suggested that the high prevalence of corticosteroid use among elite cyclists, particularly road cyclists who are at risk of trauma and infection, justifies screening tests with the measurement of basal serum cortisol, which is often decreased in this population. Other data [86] suggest that blood ACTH and blood or saliva DHEA and cortisol measurements also offer a practical approach for indirectly estimating GC intake in athletes on a long-term basis. However, one must first carefully consider the analytic technique to be used because of the high cross-reactivity of prednisolone and cortisol [47]. Moreover, the practical constraints regarding hormone circadian variations and blood conservation for ACTH analysis also need to be taken into account. Lastly, the onset of non-functional overreaching or the development of overtraining syndrome in the athlete must be ruled out.

5. Conclusion

Given the wide use of GCs in the sporting world, whether for doping or non-doping purposes, new studies on these drugs in athletes are needed for three main reasons: first, to more fully assess the causal effect(s) on performance; second, to accurately evaluate the side effects regarding the dose, the administration route and the molecule; and third, to improve current antidoping detection by taking into account inter-individual variations in GC metabolism and the possible interactions of environmental factors.

Compliance with ethical standards

NA.

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Conflicts of interest

The authors declare that they have no conflicts of interest relevant to the content of this review.

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