The clinical course after glucocorticoid treatment in patients with inflammatory bowel disease is linked to suppression of the hypothalamic–pituitary–adrenal axis: a retrospective observational study

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Abstract

Background: Adrenal insufficiency (AI) secondary to treatment with glucocorticoids (GCs) is common in patients with inflammatory bowel disease (IBD), but little is known about the relationship between AI and the clinical course in IBD. The aim of the study was to compare the clinical course in IBD patients with normal adrenal function versus patients with subnormal adrenal function.

Methods: A retrospective observational study on 63 patients with IBD who had performed a low-dose short Synacthen test (LDSST) (1 µg) immediately (1–7 days) after a standard course of GCs. A subnormal LDSST was defined as serum cortisol <550 nmol/L. Outcomes were time to next flare and fecal calprotectin levels.

Results: Sixty-three percent ($n = 40$) of the IBD patients had a subnormal LDSST. Patients who were steroid-free ($n = 41$) after the LDSST were observed for 3 years. Patients with a peak serum cortisol <400 nmol/L immediately after GC treatment had significantly longer time until the next flare-up of their IBD and tended to use a lower cumulative prednisolone dose during the study period in comparison to the other subgroups. Fecal calprotectin levels were significantly lower in patients with a peak s-cortisol <550 nmol/L versus patients with peak s-cortisol ≥550 nmol/L (median 336 µg/g (IQR 521) *versus* 955 µg/g (IQR 1867); $p = 0.012$).

Conclusions: GC-induced AI is common in patients with IBD and is associated with lower disease activity. This suggests a link between responsiveness to GC treatment and suppression of the hypothalamic–pituitary–adrenal axis in IBD.

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Introduction

Although several nonsteroid hormone options for treatment of inflammatory bowel disease (IBD) have emerged in the last decades, glucocorticoids (GCs) are still commonly used as a first-line therapy and in flare-ups of the disease.[1–3] A recent study in France showed that more than 70% of patients with IBD received a course of oral GC at least once within the first 5 years after diagnosis.[3] GC treatment is limited by side effects, leading to body changes similar to endogenous hypercortisolism (i.e. Cushing's syndrome) and hypothalamic–pituitary–adrenal (HPA) axis suppression.[4,5]

GC treatment for IBD is given in standardized schedules beginning with a high dose (prednisolone 0.5–1 mg/kg/day), which is tapered off during a period of 10–12 weeks with the purpose of allowing recovery of HPA axis function.[1,2,6–9] However, in up to 65% of the patients with IBD, HPA axis suppression persists after withdrawal of GC treatment.[6] We found no reports in the literature on the relationship between GC-induced adrenal insufficiency (AI) in patients with IBD and the response to GC treatment.

Our hypothesis is that there is an association between the clinical response to GC and concomitant side effects, manifested as a suppression of the HPA axis. As a consequence, patients who demonstrate AI after a course of GCs respond better to GC treatment. We performed a retrospective study to estimate disease activity during a 3-year period after a course of GC treatment for active IBD, and investigated the relationship between disease activity and the outcome of a low-dose short Synacthen test (LDSST) performed within 1 week of finalizing GC treatment.

Methods

Study design
A retrospective observational study.

Study population
From the hospital data records, we identified all patients with international classification of diseases (ICD) for ulcerative colitis (UC) and Crohn's disease (CD), who had performed an LDSST (*n* = 93) between the years 2005 and 2012 at the Department of Medicine, Umeå University Hospital, Sweden. Due to the reports of a high prevalence of GC-induced AI in patients with IBD,[6] there was a low threshold for testing with LDSST after a course of GCs at our clinic during this time period.

Umeå University Hospital is a primary catchment area of 150,000 citizens. During the time period, approximately 800 patients with IBD were treated at our clinic. The inclusion criterion for this retrospective observational study was an established IBD disease that had been treated with GCs and had undergone an LDSST to evaluate the HPA axis 1–7 days after a standard course of GC.

Low-dose short Synacthen test
An LDSST (1 µg) was used to test adrenal function. This test has shown excellent correlation with the insulin tolerance test[10] and is the standard test for investigation for AI in our department.[11] The patients were informed not to use oral or inhaled steroids 24 h before the test. An intravenous catheter was inserted into the forearm and a blood sample was drawn at baseline, and then at 30 and 40 min after 1 µg of Synacthen was administered intravenously. Plasma cortisol was analyzed by Cobas Cortisol (Roche Diagnostics, Rotkreuz, Switzerland), Modular E170/Cobas e601/e602.[12] The LDSST was considered normal if the peak cortisol level was at least 550 nmol/L; a peak cortisol level below 550 nmol/L was defined as AI. Furthermore, if the peak cortisol level was 400–549 nmol/L the test was judged as mild AI, whereas if the peak cortisol level was below 400 nmol/L it was judged as severe AI. In addition to the first LDSST, all additional LDSSTs were registered to estimate the time when HPA function was restored.

Medical records
Medical, surgical and laboratory records for the included patients were thoroughly reviewed for data concerning the time before and the 3 years after the first LDSST was performed. Before the first LDSST, data on estimated lifetime pre-cumulative doses of prednisolone and budesonide, IBD type, disease duration, previous treatment (surgery and medical) and the use of other GC formulas (enemas, inhalers, topical) were collected. The estimated lifetime pre-cumulative dose of GCs was defined as the sum of all oral prednisolone doses prescribed to the patient before the first LDSST. The duration of the GC course used before the first LDSST was estimated. Most patients received a standardized prednisolone treatment schedule, which started with 40 mg prednisolone daily for 1 week, followed by 30 mg prednisolone daily for 1 week, and then slowly tapered down during the additional 10 weeks. Patients who prolonged their treatment (>3 months) due to 'steroid dependency' were registered. The standardized schedule for budesonide (only used by CD patients) was 9 mg per day for 3 months followed by 6 mg per day for 3 months. The major focus of the present study was on disease activity within 3 years after the LDSST. The time until post-GC treatment flare-up was obtained from the medical records. A flare-up was defined if the doctor, due to active
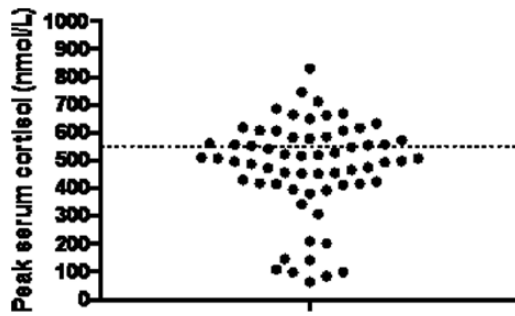
Figure 1. The distribution of peak serum cortisol in 63 patients with inflammatory bowel disease after a low-dose short Synacthen test performed after a course of glucocorticoids.

disease, intensified the therapy by increasing the 5-aminosalicylic acid (5-ASA) dose, restarted GC treatment (local or oral), initiated/intensified immunomodulators, biologics or if surgery was performed. Escalation of therapy was defined as if the patients during the observation period had started immunomodulators, biologics or had needed surgery due to IBD. At our clinic, all patients with IBD are encouraged to report by telephone as soon as they suspect a flare-up of the disease. In addition, they visit the clinic for at least annual check-ups. If the patient was in remission during the whole 3-year period, the time for the next flare-up was set to 3 years. We also registered whether the patient was treated with GC replacement therapy due to a subnormal LDSST. Standard replacement therapy used at our clinic is hydrocortisone 10 mg twice daily.

Fecal calprotectin

Fecal calprotectin (FC) level was used as an objective biomarker of gut inflammation. The samples for FC were analyzed at the Department of Laboratory Medicine, Umeå University Hospital, by the CALPRO® Calprotectin ELISA Test according to the manufacturer (Calpro AS, Lysaker, Norway) instructions. Bilevel material supplied by the manufacturer was used for quality control. The detection limit for FC is <20 µg/g. As a marker of gut inflammation, we used the first FC after the LDSST and the median value of all FC tests analyzed during the observation period.

Statistical analysis

All analyses were carried out using IBM SPSS Statistics version 23. Non-parametric tests were used for comparing ordinal scales and continuous variables (Mann–Whitney U test) and for correlations (Spearman's rank correlation coefficient). The Chi-square test was used for crosstabs analyses, and Fisher's exact test was used if there were fewer than 10 cases. Student's t test was used for parametric comparison. A two-sided p-value less than 0.05 was regarded as significant. Means and standard deviations were used for continuous variables and medians and interquartile range (IQR) were used for ordinal variables. Due to the exploratory purpose of the study we did not correct for multiple testing.

Results

Basal characteristics

Sixty-three patients (27 UC, 36 CD) fulfilled the inclusion criteria and were included in the analysis. Forty patients (63%) had a subnormal LDSST after GC treatment and 14 patients (22%) had a peak cortisol below 400 nmol/L (Figure 1). Among the patients with AI the mean peak stimulated serum cortisol was 385 ± 115 nmol/L; the distribution of peak serum cortisol value for the patients is shown in Figure 1. There were no differences in age, gender, IBD type, disease duration, the use of inhalation steroids, topical steroids, the pre-cumulative lifetime doses of prednisolone and budesonide or duration of the steroid course between patients with a subnormal *versus* a normal LDSST (Table 1). Male gender and a history of previous IBD surgery (five patients for CD and two patients for UC) was significantly more common in the subjects with a peak cortisol <400 nmol/L. Subjects with intermediate subnormal peak cortisol levels (400–549 nmol/L) had a significantly shorter time since diagnosis than the other subgroups.

Disease activity

After the LDSST, nine patients remained on a low dose of prednisolone and 12 patients remained on oral budesonide treatment for IBD. These patients and the patients with UC who had been colectomized prior to the LDSST were not included in the observational analysis of estimated disease activity. The remaining 41 patients (20 UC, 21 CD) who were steroid-free after the LDSST were retrospectively observed for 3 years (Table 2). The patients with a peak cortisol <400 nmol/L had significantly longer time until

Table 1. Basal characteristics for patients (*n* = 63) with inflammatory bowel disease investigated with low-dose short Synacthen test after a course of glucocorticoids.

	Group 1: peak s-cortisol <400 nmol/L (*n* = 14)	Group 2: peak s-cortisol 400–549 nmol/L (*n* = 26)	Group 3: peak s-cortisol ≥550 nmol/L (*n* = 23)	Group 1 *versus* Group 2 *p*-value	Group 1 *versus* Group 3 *p*-value	Group 2 *versus* Group 3 *p*-value
Median age years (SD)	44 (23)	32 (23)	36 (31)	0.32	0.59	0.83
Proportion:						
Women (*n* = 32)	21% (*n* = 3)	58% (*n* = 15)	61% (*n* = 14)	0.046*	0.040*	0.83
Men (*n* = 31)	79% (*n* = 11)	42% (*n* = 11)	39% (*n* = 9)			
Ulcerative colitis	50% (*n* = 7)	42% (*n* = 11)	39% (*n* = 9)	0.75	0.74	0.83
Crohn's disease	50% (*n* = 7)	58% (*n* = 15)	61% (*n* = 14)			
Median disease duration years (IQR)	16 (22)	5 (9)	9 (18)	0.017*	0.68	0.022*
Proportion treated with oral prednisolone	100% (*n* = 14)	85% (*n* = 22)	78% (*n* = 18)	0.278	0.135	0.716
Proportion treated with oral budesonide	0% (*n* = 0)	15% (*n* = 4)	22% (*n* = 5)	0.278	0.135	0.716
Proportion with additional steroid treatment:						
Enemas (*n* = 17)	36% (*n* = 5)	19% (*n* = 5)	30% (*n* = 7)	0.278	0.999	0.508
Inhalation (*n* = 13)	15% (*n* = 2)	24% (*n* = 6)	23% (*n* = 5)	0.689	0.689	0.999
Topical (*n* = 21)	31% (*n* = 4)	44% (*n* = 11)	27% (*n* = 6)	0.501	0.999	0.362
Duration for oral steroids prior to ST						
<3 months (*n* = 33)	64% (*n* = 9)	54% (*n* = 14)	44% (*n* = 10)	0.739	0.313	0.571
>3 months (*n* = 30)	36% (*n* = 5)	46% (*n* = 12)	56% (*n* = 13)			
Median pre-cumulative prednisolone dose (mg) (IQR)	3150 (3337)	2375 (2400)	2730 (3995)	0.149	0.379	0.487
Previous surgery (%) (*n* = 11)	43% (*n* = 6)	12% (*n* = 3)	9% (*n* = 2)	0.044*	0.035*	0.999
On immunomodulators (*n* = 29)	50% (*n* = 7)	46% (*n* = 12)	44% (*n* = 10)	0.999	0.745	0.851
On anti-TNF (*n* = 10)	29% (*n* = 4)	12% (*n* = 3)	13% (*n* = 3)	0.214	0.390	0.999

*Statistically significant.

the next flare-up of their IBD and there was a trend for smaller cumulative prednisolone dose during the study period in comparison to the other subgroups (Table 2). Seven out of eight of the patients with peak cortisol <400 nmol/L received replacement therapy with hydrocortisone. There was a non-significant negative correlation between peak cortisol levels and time to next flare-up (rs –0.289; *p* = 0.066). The first FC test after the LDSST was significantly lower in patients with peak s-cortisol <550 nmol/L (*n* = 21) than in patients with peak s-cortisol ≥550 nmol/L (*n* = 11) (median 336 µg/g (IQR 521) *versus* 955 µg/g (IQR 1867); *p* = 0.012). The median of all of a patient's FC tests during the observational period was also significantly lower in the patients with peak s-cortisol <550 nmol/L in comparison to patients with peak s-cortisol ≥550 nmol/L (median 422 µg/g (IQR 412) *versus* 820 µg/g (IQR 1955); *p* = 0.031).

Patients who received replacement therapy with hydrocortisone
Eleven of 41 patients received replacement therapy with hydrocortisone. These patients had

Table 2. Patients (*n* = 41) with inflammatory bowel disease who stopped treatment with glucocorticoids and followed retrospectively for 3 years. Patients grouped after outcome of low-dose short Synacthen test (LDSST) done after a course of corticosteroids.

	Group 1: peak s-cortisol <400 nmol/L (*n* = 8)	Group 2: peak s-cortisol 400–549 nmol/L (*n* = 18)	Group 3: peak s-cortisol ⩾550 nmol/L (*n* = 15)	Group 1 *versus* Group 2 *p*-value	Group 1 *versus* Group 3 *p*-value	Group 2 *versus* Group 3 *p*-value
Median age in years at LDSST (IQR)	34 (23)	31 (17)	30 (24)	0.892	0.825	0.901
Proportion:						
Women (*n* = 18)	0% (*n* = 0)	56% (*n* = 10)	53% (*n* = 8)	0.009*	0.019*	0.999
Men (*n* = 23)	100% (*n* = 8)	44% (*n* = 8)	47% (*n* = 7)			
Ulcerative colitis	38% (*n* = 3)	50% (*n* = 9)	53% (*n* = 8)	0.999	0.999	0.999
Crohn's disease	62% (*n* = 5)	50% (*n* = 9)	47% (*n* = 7)			
Median disease duration years (IQR)	10 (18)	5 (9)	8 (9)	0.285	0.925	0.166
Median time in months to next disease flare (IQR)	29 (24)	7 (14)	5 (10)	0.022*	0.019*	0.735
Proportion of patients who escalated therapy	25% (*n* = 2)	61% (*n* = 11)	33% (*n* = 5)	0.202	0.999	0.166
Proportion of patients treated with oral hydrocortisone in physiological doses	88% (*n* = 7)	17% (*n* = 3)	7% (*n* = 1)	0.001*	<0.001*	0.607
Median post-cumulative prednisolone dose (mg) (IQR)	0 (800)	370 (2800)	1015 (2000)	0.131	0.397	0.901
Median of the first fecal calprotectin test (µg/g) after the LDSST (IQR)	433 (1951)	250 (506)	955 (1867)	0.446	0.320	0.008*
Median of all fecal calprotectin tests (µg/g) after the LDSTT (IQR)	290 (551)	439 (379)	830 (1955)	0.968	0.145	0.044*
*Statistically significant.						

significantly longer time to next flare-up than patients without hydrocortisone (median 23 months (IQR 32) *versus* 8 months (IQR 10); *p* = 0.050) but there were no differences in cumulative prednisolone dose or FC test levels between the patients with and without hydrocortisone treatment.

Restoration of HPA function
Ten out of 14 patients (71%) with GC-induced AI (peak cortisol <550 nmol/L) still showed subnormal HPA function when retested (3–15 months after first LDSST). Seven out of these 10 patients had received replacement therapy in physiological doses but none of the patients had received courses of GCs due to flare-ups. These 10 patients remained insufficient in their cortisol production until at least 3.1 ± 2.5 years (mean ± SD) after the first LDSST.

Discussion
We could verify a high incidence of GC-induced AI in patients with IBD, in line with earlier studies.[6] This study suggests an association between GC-induced AI and lower disease activity in patients with IBD after GC treatment. This is a novel finding and requires verification in prospective studies. The association was most obvious in patients with more severe AI. In line with this, patients with AI defined by a peak serum cortisol <550 nmol/L had significantly lower FC values after GC treatment compared to patients with normal adrenal function.

The subjects in our study showed a large variability in peak cortisol after LDSST (Figure 1). A plausible explanation for the variability in post-GC-exposure AI is the wide inter-individual variability in GC sensitivity.[13] Such variability could also explain the finding that patients with AI after

GC exposure had less inflammatory activity in the gut as estimated by time to next flare-up and FC, which may thus imply a stronger anti-inflammatory response to the given standard GC treatment. It is well known that if inflammation resolves in the gut mucosa it predicts a favorable clinical outcome in patients with IBD.[14] A patient with a higher GC sensitivity thus has better odds to achieve mucosal healing.

A recent review thoroughly presents putative genetic mechanisms for GC resistance in patients with IBD.[15] A decreased response to GCs – that is 'GC resistance' – is common in inflammatory diseases. For example, 30% of patients with rheumatoid arthritis[16] and 16–20% of patients with IBD were reported to be resistant to GC.[17,18] Factors responsible for individual GC sensitivity are steroid bioavailability in the affected organ, GC receptor expression and affinity and GC receptor signaling.[13] Polymorphisms in the GC receptor gene (NR3C1) may influence the formation of the GC receptor (GR) and the GR–GC complex and change the expression of target genes. Several alterations in the NR3C1 gene have been described, notably the *Bcl*I polymorphism, and associated to GC response.[19] An increased sensitivity to GCs via this polymorphism has been suggested to predict GC treatment response in children with IBD, but this has not been confirmed in other studies.[15] Other genes that may play a role in GC sensitivity are the ARCB1/MDR1 gene and the IP013 gene, involved in cytoplasmic GC transport.[15] Furthermore, a gene polymorphism in the GC-induced transcript 1 (GLCCI1) gene has been related to variable disease activity and therapeutic response to GC in asthma and rheumatoid arthritis.[13,20] This gene polymorphism in the GR has not been studied in patients with IBD.

Despite the established term 'steroid-dependent', which is used to classify patients with IBD in clinical trials,[21–23] GC has failed to be effective overall in patients with CD as a maintenance treatment,[24] but this does not rule out the possibility that a subset of patients (who are sensitive to GC) may benefit from such treatment. Perhaps also small doses (physiological doses) could benefit 'glucocorticoid sensitive' patients in analogy to what we observed in the patients with GC-induced AI in our study, where the majority of patients in the group with more severe AI were on long-term hydrocortisone treatment. One can also hypothesize that some

patients who are classified as 'steroid-dependent' have GC-induced AI and therefore have difficulties terminating steroid treatment. However, long-term treatment with GC is also restricted by side effects such as osteoporosis and infections.[25] The identification of a marker that could determine whether a patient is sensitive or resistant to GC treatment early in the course of IBD might improve tailoring of the treatment for patients with IBD. A patient with decreased sensitivity to GC treatment could receive an alternative treatment (immunomodulators or biologics) earlier instead of repeated courses of GCs; a patient who is sensitive to GCs could perhaps receive a lower treatment dose. Interestingly, a pilot study found an association between *in-vitro* measurement of T lymphocyte GC sensitivity and clinical response to GCs in subjects with UC.[26] Whether a LDSST or basal serum cortisol before steroid treatment can predict GC responsiveness is not known. In contrast, there was no difference in HPA axis suppressibility measured by a dexamethasone suppression test, between GC resistant and sensitive asthma patients.[27] Similar studies are therefore of interest in subjects with different types of IBD, as there is a lack of useful predictors for development of AI after GC therapy.[4]

The present study confirms the high incidence of GC-induced AI in patients with IBD seen in other studies.[6,28–31] The present study and others[4] also show that in a substantial number of patients with induced AI, the subnormal adrenal function persists sometimes for years after the withdrawal of GC treatment. Desramé and colleagues found a mean recovery time of adrenal function of 7.2 months (range 1–18 months) using a 250 μg Synacthen test.[6] In the present study, using an LDSST, we found an even longer time to normalization of adrenal function (mean 3.1 years). The consequence for patients with IBD living with a dysfunctional HPA axis was studied by Minderhoud and colleagues.[32] The authors found no association between fatigue in quiescent IBD and AI, but unfortunately all patients who had taken steroids within 12 months before the study were excluded, and only a few patients were assessed by an LDSST.

In some clinical settings, an LDSST for every patient with IBD treated with GCs may be impractical; instead, an annual test of baseline serum cortisol, as has been suggested for patients with asthma taking inhaled corticosteroids, could be feasible. A baseline serum cortisol

<100 nmol/L strongly suggests the need for oral hydrocortisone treatment, and a serum cortisol between 100–348 nmol/L suggests further investigation with an LDSST.[11,33]

Limitations

This is a retrospective observational study, and the decision to test for HPA axis function was made by clinical judgment and not in a standardized study protocol, which makes it difficult to control for possible confounders and selection bias. For example, the patients with replacement therapy tended to be older and may therefore present with a more quiescent disease than younger patients. As this is a retrospective study, the information that stated why the physician had ordered an LDSST was in most cases lacking and the precumulative GC doses varied significantly.

The LDSST has a high sensitivity for AI, constructed to detect subtle HPA axis insufficiency.[11] Therefore, the subtle HPA axis insufficiency detected in a large proportion of our patients may have limited clinical implications.

In conclusion, our study verifies that AI after standard GC treatment for IBD is common. Importantly, suppression of the HPA axis is associated with lower inflammatory activity in the gut. We suggest that a low threshold to test for AI after a course of GCs for IBD is informative about the clinical course, including the possible need for GC replacement treatment. Prospective studies are needed to define the clinical consequences of GC-induced AI in patients with IBD.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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