Metformin prevents metabolic side effects during systemic glucocorticoid treatment

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Abstract

Objectives: Patients receiving glucocorticoid treatment are prone to develop metabolic complications. In preclinical studies, metformin prevented the development of the metabolic syndrome during glucocorticoid excess. We herein investigated the metabolic effect of metformin during glucocorticoid treatment in non-diabetic patients.

Methods: In a double-blind, placebo-controlled trial, patients starting glucocorticoid treatment (prednisone, prednisolone or methylprednisolone) for four weeks were randomised to concomitantly receive metformin (850 mg once daily for one week followed by 850 mg twice daily for three weeks) or placebo. All patients underwent a standardised oral glucose tolerance test at baseline and after four weeks. The primary endpoint was change in the 2-h area under the curve (AUC) of glucose during the oral glucose tolerance test between baseline and four weeks.

Results: 29 of 34 randomised non-diabetic patients completed the trial (17 metformin and 12 placebo). In patients allocated to placebo, median glucose 2-h AUC increased from baseline to four weeks (836 (IQR 770–966) to 1202 (1009–1271) mmol/L per min; $P=0.01$). In contrast, glucose levels remained similar to baseline in the metformin group (936 (869–1003) to 912 (825–1011) mmol/L per min; $P=0.83$). This change within four weeks was different between both groups ($P=0.005$). Glucocorticoid equivalent doses were similar in both groups (placebo: 980.0 (560.0–3259.8) mg/28 days; metformin: 683.0 (437.5–1970.5) mg/28 days; $P=0.26$).

Conclusions: In this first randomised controlled trial of metformin targeting metabolic complications in patients needing glucocorticoid therapy, we observed a beneficial effect of metformin on glycaemic control. Metformin thus seems to be a promising drug for preventing metabolic side effects during systemic glucocorticoid treatment.

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Introduction

Up to 2.5% of the adult western population receive systemic glucocorticoid therapy, mostly for inflammatory conditions (1). Diabetes mellitus, dyslipidaemia, central obesity and hypertension are well-known and common side effects of glucocorticoid treatment (2, 3). Especially, diabetes mellitus is a recurring problem with a reported prevalence of up to 40% in patients receiving long-term

glucocorticoid treatment (4, 5, 6, 7, 8). Even if used as an antiemetic drug in cancer patients, glucocorticoids clearly increased the risk of diabetes mellitus (8). In contrast to other well-known side effects of glucocorticoids, such as gastric ulcer disease, no randomised controlled evidence exists that has investigated the potential therapeutics for the treatment of metabolic side effects of glucocorticoids.

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Many of the changes seen in glucocorticoid excess, such as gluconeogenesis, correspond to metabolic steps regulated by adenosine monophosphate-activated protein kinase (AMPK) (9). AMPK is a key regulator of energy metabolism and mediator of several hormones affecting appetite and metabolism (10). Metformin, a widely used drug for prevention and treatment of diabetes mellitus type 2, exerts most of its beneficial effects on metabolism through the activation of AMPK (11, 12). We have shown previously that glucocorticoid treatment changes AMPK activity in human adipocytes *in vitro* and reduced AMPK activity is seen in adipose tissue of patients with Cushing's syndrome (13, 14). Importantly, metformin reversed the effects of corticosteroids on AMPK *in vitro* both in primary hypothalamic cell culture as well as in adipocytes, suggesting that metformin and glucocorticoids influence the AMPK signalling pathway in opposite ways and that the metformin effect is able to override the cortisol effect (13, 15). *In vivo* studies showed that treatment with an AMPK activator prevented glucocorticoid-induced increase in glucose levels, hepatic glycogen production and hepatic steatosis in rats (16). Furthermore, metformin efficiently prevented the dexamethasone-induced deterioration of glucose metabolism in mice and horses (17, 18). These data suggest that metformin treatment could be beneficial in preventing metabolic complications in patients receiving long-term corticosteroid treatment.

In the first double-blind, randomised, placebo-controlled trial, we investigated the metabolic effects of metformin during glucocorticoid treatment in non-diabetic patients starting treatment with corticosteroids for at least 4 weeks.

Materials and methods

Study design

In this randomised, placebo-controlled, double-blind study, we included patients starting glucocorticoid treatment for at least 4 weeks. Participants were recruited at several departments at the University Hospital Basel and the Cantonal Hospital Aarau from August 2010 to March 2015. Patients were randomised in a 1:1 ratio to receive either metformin 850mg daily p.o. for one week followed by 850mg twice daily p.o. for another three weeks or identical placebo (Merck, Germany). The study was terminated after four weeks in all patients, also in cases where glucocorticoid treatment was continued. The study was registered at Clinicaltrials.gov NCT01187849.

Patients

Inclusion criterion was a newly initiated treatment with prednisone ≥ 7.5 mg or an equivalent glucocorticoid for at least 4 weeks. Glucocorticoid tapering was determined by the treating physicians. Exclusion criteria were pre-existing diabetes mellitus (according to the American Diabetes Association criteria); renal insufficiency (estimated glomerular filtration rate using the CKD-EPI formula above 60mL/min/1.73); severe conditions affecting renal function (e.g. dehydration, fever and severe infection); severe conditions causing tissue hypoxia (e.g. acute cardiac or respiratory insufficiency); scheduled examination using intravascular contrast agent containing iodine; alcohol consumption of more than 40g/day (male) or 20g/day (female); known allergy to metformin; pregnancy or breast feeding and any condition compromising the ability of the subject to give written informed consent.

The study was approved by the ethical committees of the participating hospitals and Swissmedic and was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participating subjects before randomisation.

Study assessment

At baseline and after four weeks, a standardised 2-h 75g oral glucose tolerance test was performed. After an overnight fast, baseline blood samples for fasting glucose, insulin, HbA1c, a full lipid profile and safety blood measurements were taken directly before ingestion of glucose. Additional blood samples for glucose were taken 30, 60, 90 and 120min thereafter. Physical examination and urine analysis were performed, and doses of glucocorticoids were assessed at both visits. After one week, a telephone call took place to assess the compliance, adverse events and dosage of glucocorticoids. Three forms of glucocorticoids were prescribed: prednisone, prednisolone and methylprednisolone (Supplementary Table 1, see section on supplementary data given at the end of this article). If needed, doses of glucocorticoids, e.g. methylprednisolone, were converted to equivalent doses of prednisone (19). Due to glucocorticoid tapering, cumulative glucocorticoid doses were calculated as follows: area under the curve was calculated using glucocorticoid doses at baseline, one and four weeks. The average daily prednisone dose was calculated as the area under the curve of the 28 study days.

Plasma glucose and lipids were measured with enzymatic assays (cobas modular analyzer, Roche Diagnostics). Serum insulin and c-peptide were assessed using immune assays (IMMULITE 2000, Siemens). HbA1c was analysed in EDTA plasma with high-performance liquid chromatography (G8 HPLC Analyzer, Tosho Bioscience, San Francisco, CA, USA). Measurements of all blood parameters were taken in the routine central laboratory unit of the University Hospital Basel. The reported HOMA index was calculated according to Matthews *et al.* (20). Body impedance analysis (Body Impedance Analyzer Model BIA 101, Akern Srl, Florence, Italy) was performed to assess body composition and energy expenditure.

A randomisation list based on single sequence of random assignments was created by the Pharmaceutical Unit of the University Hospital Basel. Patients as well as study personnel were blinded to the medication allocation.

Study end points

The predefined primary endpoint was the change in the area under the concentration–time curve (AUC) for glucose during the 75g oral glucose tolerance test between baseline and four weeks. Predefined secondary endpoints included change in fasting glucose levels, glycated haemoglobin levels (HbA1c), Homeostatis Model Assessment (HOMA) index, fasting lipid levels, body mass index, body composition and waist/hip ratio.

Statistical analysis

According to the protocol, the primary analysis followed the intention-to-treat principle, i.e. patients with complete follow-up were analysed in the groups to which they were randomised. Patients in the metformin group were expected to have unchanged 2-h glucose levels after ingestion of 75g glucose, whereas patients in the

placebo group would have an increase of approximately 25%. Based on these assumptions, a sample size of 66 patients (33 per arm) was calculated to detect a significant difference between these distributions with a power of 90% at the two-sided 5% level. Discrete variables are expressed as counts (percentages) and continuous variables as median (interquartile range (IQR)). To compare changes across treatment groups the Mann–Whitney *U* test was used for continuous data and the Fisher's exact test for categorical data. The Wilcoxon signed-rank test was used for comparisons within subjects. Incremental AUC for glucose values (during 120 min of a standardised oral glucose tolerance test) and glucocorticoid doses (during 28 days of study duration) was calculated using the trapezoid rule. To adjust for relevant covariates, linear regression analyses were employed. *P* value <0.05 was defined as significant. Data were analysed using statistical software (Statistical Package for Social Sciences IBM SPSS, version 22). Figures were drawn using GraphPad Prism (GraphPad Software Inc.).

Results

Baseline characteristics

34 individuals were randomly assigned (1:1) to receive metformin (*n*=20) or placebo (*n*=14). In the metformin group, two patients withdrew from the study due to gastrointestinal symptoms and vertigo respectively; another patient was lost to follow-up after the baseline visit. In the placebo group, one patient did not receive glucocorticoids and one patient was lost to follow-up. A total of 17 subjects in the metformin group and 12 subjects in the placebo group completed the trial (Fig. 1). Patients in both treatment groups were well matched for baseline characteristics (Table 1). Baseline glucocorticoid doses were similar in both groups (metformin: 35.0 (11.3–50.0) mg/day; placebo: 30.0 (20.0–362.5) mg/day; *P*=0.48). A comparison between patients completing the trial (*n*=29) and patients dropping out (*n*=5) showed no

Figure 1
Enrolment of participants.

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Table 1 Baseline characteristics (including 5 patients with missing outcome variables); median values (IQR).

	Placebo (n=14)	Metformin (n=20)	P value
Male sex (%)	35.7	70.0	0.08
Age (years)	56.5 (46.5–67.8)	58.0 (35.8–74.3)	0.69
BMI (kg/m ²)	25.7 (20.6–27.5)	24.2 (21.6–28.6)	0.69
Waist/hip ratio	0.9 (0.8–1.0)	1.0 (0.9–1.0)	0.24
Systolic blood pressure (mmHg)	129 (120–147)	132 (116–139)	0.96
Diastolic blood pressure (mmHg)	80 (71–86)	75 (70–80)	0.26
HbA1c (%)	5.7 (5.4–5.9)	5.4 (5.3–5.8)	0.32
HbA1c (mmol/mol)	39.0 (36.0–40.0)	36.0 (34.0–40.0)	0.32
Fasting glucose (mmol/L)	5.0 (4.6–5.3)	4.8 (4.6–5.3)	0.77
Fasting insulin (mIU/L)	5.8 (2.5–11.1)	8.6 (4.3–14.8)	0.29
HOMA index	1.0 (0.5–2.0)	1.9 (1.0–3.4)	0.18
Glucose 2 h AUC (mmol/L per min)	864.8 (782.6–1012.1)	937.5 (872.3–991.1)	0.34
Triglycerides (mmol/L)	1.1 (0.9–1.2)	1.3 (0.9–1.7)	0.32
Total cholesterol (mmol/L)	4.8 (4.4–5.2)	4.8 (4.3–5.6)	0.64
HDL cholesterol (mmol/L)	1.4 (1.0–1.7)	1.2 (1.0–1.4)	0.48
LDL cholesterol (mmol/L)	2.9 (2.6–3.1)	3.1 (2.5–3.8)	0.27
Creatinine (umol/L)	67.0 (60.8–75.5)	79.0 (59.8–87.3)	0.27
Prednisone dosage (mg/day)	30.0 (20.0–362.5)	35.0 (11.3–50.0)	0.48
Basal metabolic rate (kcal)	1665 (1423–1923)	1730 (1593–1823)	0.60
Fat free mass (kg)	57.0 (47.2–62.9)	57.9 (50.6–63.3)	0.70
Fat mass (kg)	16.9 (9.3–22.1)	14.6 (8.5–21.2)	0.77

difference in baseline criteria except for glucocorticoid doses (complete: 40.0 (20.0–95.0)mg/day; drop out: 12.5 (10.0–26.3)mg/day, $P=0.03$) (Supplementary Table 2). AUC prednisone doses in patients completing the trial remained similar in both groups throughout the study (metformin: 683.0 (437.5–1970.5)mg/28 days; placebo: 980.0 (560.0–3259.8)mg/28 days, $P=0.26$). Indications for glucocorticoid treatment are presented in Table 2. Concomitant medication with potential effect on glucose

and/or lipid metabolism is listed in Supplementary Table 3. Due to slow study recruitment and time of expiry of study drug, the study had to be prematurely terminated. This led to fewer study participants than intended and to an unbalanced randomisation.

Effect of metformin on glycaemia

Two-hour AUC glucose remained similar from baseline to four weeks in the metformin group ($P=0.83$), whereas it was increasing in the placebo group ($P=0.01$; Fig. 2A, B and C). Accordingly, the primary endpoint of 2-h AUC glucose change within four weeks was different between both groups ($P=0.005$; Table 3; Fig. 2D). After adjustment for gender, cumulative glucocorticoid dose and HbA1c, treatment group remained strongly associated with 2-h AUC glucose (adjustment for gender: treatment group $P=0.006$, $R^2=0.32$; adjustment for glucocorticoid dose: treatment group $P=0.003$, $R^2=0.33$; adjustment for HbA1c: treatment group $P=0.002$, $R^2=0.38$). Among the secondary endpoints, the change in fasting glucose, fasting insulin and HOMA index were different between the two groups ($P=0.01$, $P=0.003$ and $P=0.035$ respectively; Fig. 3A, B, C, D, E and F). We observed no change in HbA1c in the treatment and placebo groups during the study period ($P=0.64$; Fig. 3G and H).

Furthermore, we aimed to differentiate between responders and non-responders to metformin. As the 2-h AUC glucose increase in the placebo group was 40.3

Table 2 Indications for glucocorticoid treatment (including 5 patients with missing outcome variables).

Diagnosis	Placebo (n=14)	Metformin (n=20)
Arthritis	2	2
Vasculitis	1	3
Polymyalgia rheumatica	1	2
Eosinophilic fasciitis	1	
Lupus erythematoses	1	
Sarcoidosis		2
Sclerosing lymphadenopathy	1	
Cutaneous sclerosis		1
Morbus-Wegener	1	
Alopecia areata		1
Pemphigus	2	1
Eczema		1
Metastatic prostate carcinoma		1
Astrocytoma	1	
Organizing pneumonia		1
Allergic bronchopulmonary aspergillosis		1
Myasthenia gravis		1
Endocrine orbitopathy	3	2
Scleritis		1

Figure 2

Change in glucose during oral glucose tolerance test.

(A) Plasma glucose values during oral glucose tolerance test at baseline and after four weeks in placebo-treated patients.

(B) Glucose values during oral glucose tolerance test at baseline and after four weeks in patients treated with metformin.

(C) 2-h AUC glucose in both study groups at baseline and after 4 weeks.

(D) Differences in 2-h AUC glucose between baseline and four weeks in each study group.

Data represent median values error bars indicate interquartile ranges. * P value <0.05 .

(18.9–51.0)%, we allocated patients in the metformin group with an increase below 20% to responders, and patients with an increase equal and above 20% to non-responders. This resulted in three patients, who were classified as non-responders. Their baseline characteristics are listed in [Supplementary Table 4](#).

Effect of metformin on lipids

Fasting triglyceride levels did not change during the trial, and there was no difference between groups ($P=0.30$). Total cholesterol levels increased only in the placebo group ($P=0.02$) while remaining stable in the metformin group ($P=0.10$). No difference in cholesterol between groups was observed ($P=0.15$). HDL levels increased in both groups compared to baseline (metformin: $P<0.0001$; placebo: $P=0.003$). The HDL increase over the four weeks was more pronounced in the metformin group ($P=0.04$). LDL levels did not change during the trial, and there was no difference between groups ($P=0.71$; [Table 3](#)).

Effect of metformin on body composition and energy expenditure

We identified no change in BMI, waist-to-hip ratio, basal metabolic rate, fat free mass and fat mass during the study period; there was no difference across treatment groups ([Table 3](#)).

Adverse events

Gastrointestinal symptoms were present in 20.0% of patients in the metformin and in 21.4% of patients in the placebo group ([Supplementary Table 5](#)). All gastrointestinal symptoms were either mild or moderate. There was no difference between groups ($P=0.99$). In the metformin group, one subject discontinued the study due to gastrointestinal symptoms, and another patient discontinued due to vertigo. One subject in the metformin group was hospitalised for further evaluation of the underlying disease (vasculitis) after study inclusion. The hospitalisation was rated as serious adverse event unrelated to the study drug.

Discussion

In this trial, with non-diabetic patients receiving systemic glucocorticoids, we demonstrate for the first time that preventive metformin treatment is superior to placebo with respect to glycaemic control as indicated by 2-h glucose AUC, HOMA index, fasting glucose and fasting insulin. This effect was consistent after adjustment for gender, cumulative glucocorticoid dose and HbA1c. Although HDL cholesterol levels increased in both groups during GC treatment, we did not observe a change in triglycerides, LDL, body weight or body composition.

Despite the very frequent use of glucocorticoids and the well-known detrimental impact on glucose metabolism, hardly any randomised controlled trials have investigated the prevention of glucocorticoid-induced diabetes ([21](#), [22](#), [23](#), [24](#)). In one of these trials, troglitazone prevented deterioration of glucose metabolism during glucocorticoid treatment, whereas pioglitazone and metformin had no effect ([25](#)). Noteworthy, troglitazone can no longer be used as it was withdrawn from the market. Compared to our study, duration of metformin and steroid treatment was very short and metformin dose was low. Two other randomised controlled trials targeting the GLP-1 pathway produced heterogeneous results ([26](#), [27](#)). Importantly, all three studies were performed in individuals without

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Table 3 Primary and secondary endpoints; median values (IQR); for each parameter, change from baseline was compared between groups (metformin vs placebo) using the Mann–Whitney *U* test and within-groups using the Wilcoxon signed-rank test.

	No. of patients on metformin vs placebo	Placebo	Metformin	Between group <i>P</i>
Glucose 2h AUC (mmol/L/min)	17 vs 8			0.005
Baseline		835.5 (769.9–966.0)	936.0 (869.3–1002.8)	
4 weeks		1202.3 (1008.8–1270.9)	912.0 (825.0–1011.0)	
Within-group <i>P</i>		0.01	0.83	
HOMA-index	17 vs 9			0.035
Baseline		1.0 (0.4–1.4)	2.2 (1.0–3.6)	
4 weeks		1.5 (0.8–2.0)	1.1 (0.6–2.7)	
Within-group <i>P</i>		0.07	0.04	
Fasting glucose (mmol/L)	17 vs 11			0.01
Baseline		4.8 (4.4–5.3)	4.8 (4.6–5.3)	
4 weeks		5.3 (4.5–5.6)	4.6 (4.2–5.0)	
Within-group <i>P</i>		0.07	0.04	
Insulin (mIU/L)	17 vs 10			0.003
Baseline		5.4 (2.3–8.3)	9.3 (4.5–15.6)	
4 weeks		6.8 (4.0–13.4)	5.7 (3.3–13.4)	
Within-group <i>P</i>		0.07	0.06	
HbA1c (%)	16 vs 12			0.64
Baseline		5.7 (5.3–5.9)	5.4 (5.3–6.0)	
4 weeks		5.8 (5.3–5.9)	5.5 (5.3–6.0)	
Within-group <i>P</i>		0.19	0.48	
HbA1c (mmol/mol)	16 vs 12			0.64
Baseline		39.0 (34.0–41.0)	36.0 (34.0–42.0)	
4 weeks		40.0 (34.0–41.0)	37.0 (34.0–42.0)	
Within-group <i>P</i>		0.19	0.48	
Triglycerides (mmol/L)	17 vs 11			0.30
Baseline		1.1 (0.8–1.1)	1.3 (0.9–1.6)	
4 weeks		1.2 (0.9–1.3)	1.2 (1.0–1.4)	
Within-group <i>P</i>		0.17	0.65	
Total cholesterol (mmol/L)	17 vs 11			0.15
Baseline		4.8 (4.5–5.1)	4.8 (4.2–5.7)	
4 weeks		5.6 (4.8–6.9)	5.4 (4.6–6.4)	
Within-group <i>P</i>		0.02	0.10	
HDL (mmol/L)	17 vs 11			0.04
Baseline		1.5 (1.0–1.6)	1.3 (1.1–1.5)	
4 weeks		2.0 (1.7–2.8)	1.7 (1.3–1.9)	
Within-group <i>P</i>		0.003	<0.0001	
LDL (mmol/L)	17 vs 11			0.71
Baseline		2.9 (2.6–3.1)	3.0 (2.3–3.9)	
4 weeks		3.0 (2.7–3.4)	3.0 (2.5–3.8)	
Within-group <i>P</i>		0.53	0.83	
BMI (kg/m ²)	17 vs 12			0.30
Baseline		25.7 (21.9–26.4)	23.7 (20.9–28.7)	
4 weeks		25.5 (21.4–27.4)	23.6 (21.1–28.7)	
Within-group <i>P</i>		0.72	0.26	
Waist-to-hip ratio	16 vs 9			0.36
Baseline		0.9 (0.8–1.0)	1.0 (0.9–1.0)	
4 weeks		1.0 (0.9–1.0)	1.0 (0.9–1.0)	
Within-group <i>P</i>		0.17	0.93	
Basal metabolic rate (Kcal)	14 vs 10			0.95
Baseline		1665 (1523–1888)	1730 (1550–1835)	
4 weeks		1620 (1418–1952)	1745 (1513–1820)	
Within-group <i>P</i>		0.65	0.55	

(Continued)

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Table 3 Continued.

	No. of patients on metformin vs placebo	Placebo	Metformin	Between group <i>P</i>
Fat free mass (kg)	14 vs 10			0.38
Baseline		57.0 (47.5–62.3)	58.3 (52.9–63.9)	
4 weeks		54.7 (41.6–63.2)	57.7 (51.5–64.7)	
Within-group <i>P</i>		0.37	0.95	
Fat mass (kg)	14 vs 10			0.98
Baseline		16.9 (10.4–21.3)	14.6 (9.8–22.3)	
4 weeks		19.2 (12.1–22.8)	17.1 (9.5–22.9)	
Within-group <i>P</i>		0.59	0.35	
AUC prednisone dosage (mg/28 days) ^a	17 vs 12	980.0 (560.0–3259.8)	683.0 (437.5–1970.5)	0.26

^aPrednisone dosage was calculated as area under the curve using glucocorticoid doses at baseline, one and four weeks.

inflammatory disease, thus not representing the patients in need of glucocorticoid treatment. As inflammation is a known mediator of insulin resistance, it is important to investigate the potential benefits of metformin in an appropriate study population (28). Therefore, more convincing strategies to prevent metabolic side effects of glucocorticoid treatment in patients indeed suffering from inflammatory diseases are needed.

From a pathophysiological point of view, metformin is an attractive preventive treatment strategy in patients receiving corticosteroids. Metformin's mode of function has been extensively discussed, and several mechanisms such as inhibition of glycerol phosphate dehydrogenase, enhanced action of glucagon-like-peptide 1 or antagonism of glucagon have been proposed (29, 30, 31, 32). Overall, the activation of AMPK seems to play an important role (11, 12, 33, 34). AMPK is generally considered to be a master regulator of energy metabolism, sensing energy depletion and activating energy-generating pathways (10). Glucocorticoids have been shown to inhibit AMPK activity and, importantly, metformin was able to reverse this inhibitory effect of glucocorticoids on AMPK *in vitro* and in animal studies (13, 14, 16).

In accordance with these experimental data, our study showed that metformin favourably influences several side effects of glucocorticoid therapy. We found that metformin prevented an increase of 2-h glucose AUC indicating preservation of glucose tolerance. The HOMA index, a marker of insulin resistance, clearly improved in the metformin group, whereas deterioration was observed in the placebo group. Fasting glucose levels decreased in the metformin group, whereas increased in the placebo group during the study period. Moreover, change in fasting insulin was different between groups. Still, we could not identify a difference in HbA1c. However, our study was conducted over four weeks while HbA1c reflects average blood glucose over the previous 8–12 weeks (35).

Therefore, we speculate that a longer study duration could show a beneficial effect on HbA1c.

Compared to glucose metabolism, the role of glucocorticoids in lipid metabolism is more controversial. Patients with endogenous overproduction of glucocorticoids are prone to develop dyslipidaemia (2). Similarly, glucocorticoid administration has been associated with the deterioration of lipid metabolism (36). Interestingly, in a large observational study, glucocorticoids were associated with higher HDL levels and glucocorticoid treatment was shown to normalise HDL levels in rheumatoid arthritis (37, 38, 39). This positive effect of glucocorticoids may be due to the reduction of the inflammatory burden rather than a direct impact on lipid metabolism.

Although the role of glucocorticoids on lipids remains unclear, metformin presumably has a beneficial effect by decreasing triglycerides and LDL cholesterol while increasing HDL cholesterol independent of glucose metabolism (40, 41, 42). In our trial, we did not observe a change in triglycerides or LDL; however, HDL cholesterol levels increased in both study groups. This finding may be due to a direct effect of glucocorticoids or rather an indirect effect of lowering the inflammatory status.

Central obesity is another characteristic feature of chronic high-dose glucocorticoid exposure (43, 44). In the Diabetes Prevention Program Study, metformin reduced body weight for around 2 kg during a 2-year study period in diabetic patients (45). Thus, metformin exerts opposite effects to glucocorticoids regarding weight.

In our trial, four weeks of glucocorticoid treatment did not result in change of body composition or waist/hip ratio in either study groups. Consequently, no effect of metformin could be observed. Possibly, the study duration was too short and the sample size was too small; longer treatment duration with corticosteroids and metformin or placebo respectively, may provide different results.

Figure 3

Change in HOMA index, fasting glucose, fasting insulin and HbA1c. (A) HOMA index at baseline and after four weeks for both study groups. (B) Differences in HOMA index between baseline and four weeks in each study group. (C) Fasting glucose at baseline and after four weeks in each study group. (D) Differences in fasting glucose between baseline and four weeks in each study group. (E) Fasting insulin at baseline and after four weeks in each study group. (F) Differences in fasting insulin at baseline and after four weeks in each study group. (G) HbA1c at baseline and after four weeks in each study group. (H) Differences in between baseline and four weeks in each study group. Data represent median values, error bars indicate interquartile ranges. **P* value <0.05.

Gastrointestinal adverse events occurred in similar number in both treatment groups. Several other studies found metformin to be safe and well tolerated (46).

Our study has some limitations. First, the study was prematurely terminated, which led to a rather small sample size. This was due to a combination of slow and difficult recruitment and time to expiry of the trial drug. Nevertheless, due to higher than expected effect of metformin, the sample size was sufficient to demonstrate a significant effect on the primary and several secondary endpoints. As we show a highly significant result, lack of statistical power is not an issue. Second, more and predominantly male patients were in the metformin group. Third, causes of glucocorticoid administration were very variable, and the study design did not allow stratification of diseases. Although overall glucocorticoid doses were not different between groups, some participants in the placebo group received the highest doses. Importantly, variability of indications and administration of glucocorticoid treatment mirror real life practice and make the results more generalisable. Fourth, baseline HbA1c was slightly higher in the placebo group, potentially putting these patients at higher risk for development of diabetes. Importantly, the difference in HbA1c was not significant between groups, and the primary endpoint remained highly significant after adjustment for HbA1c.

Our results indicate that metformin prevents deterioration of glucose metabolism if treatment is timed with the initiation of glucocorticoids. This study provides the basis for metformin as a preventive treatment in patients newly receiving glucocorticoid therapy. Further studies are needed to test if occurrence of glucocorticoid-induced diabetes can be reduced and if metformin has similar beneficial effects in patients with continuous glucocorticoid treatment. As our patient number was too small to identify unique characteristics distinguishing responders from non-responders, this remains to be investigated in future studies.

In summary, this is the first randomised controlled trial showing that metformin has a beneficial preventive effect on glycaemic control in non-diabetic patients receiving systemic glucocorticoid therapy.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0653>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

M C-C designed the study. E S, S M, K T, N N and M B conducted the experiments. E S analysed the data. E S, S M and M C-C wrote the manuscript. K T, I P, P S, B M and M K reviewed and edited the manuscript. M C-C is the guarantor of the study and, as such, takes responsibility for the contents of this article.

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