

Metformin prevents metabolic side effects during systemic glucocorticoid treatment

BACKGROUND:

- DM, dyslipidemia, central obesity & HTN are well-known and common side effects of glucocorticoid treatment
- Many of the changes seen in glucocorticoid excess, such as gluconeogenesis, correspond to metabolic steps regulated by adenosine monophosphate-activated kinase (AMPK)
- Metformin, exerts most of its beneficial effects on metabolism via activation of AMPK
- 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.

OBJECTIVE

- To investigate the metabolic effect of metformin during glucocorticoid treatment in non-diabetic patients.

METHODS

- **Design:** double blind, randomized, placebo controlled, parallel trial; Duration: 4 weeks
- **Inclusion criteria:** Newly initiated treatment with prednisone ≥ 7.5 mg or an equivalent glucocorticoid for at least 4 weeks
- **Exclusion criteria:** preexisting DM, renal insufficiency, severe conditions affecting renal function (e.g. dehydration); 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 40 g/day (male) or 20 g/day (female); known allergy to metformin; pregnancy or breast feeding and any condition compromising the ability of the subject to give written informed consent.
- **Primary outcome measure:** change in the 2-h area under the curve (AUC) of glucose during the 75g oral glucose tolerance test between baseline and four weeks
- **Secondary outcome measures:** change in fasting glucose levels, HbA1c, HOMA index, fasting lipid levels, body mass index, body composition and waist/hip ratio.
- 34 patients were randomized in a 1:1 ratio to receive either
 - (20 pts) metformin 850 mg daily X 1 week followed by 850 mg BID X 3 weeks
 - (14 pts) identical placebo
- 90 % power if metformin group had an unchanged 2-h glucose levels after OGTT and placebo pts had a 25% increase with sample size of 66 patients (33 per arm), but only 34 patients were enrolled, so a 90% power was not met
- Data handling method was listed as ITT but was actually reported as per-protocol

RESULTS

- 29 of 34 non-diabetic patients completed the trial (17 metformin and 12 placebo)
- **Primary outcome measure:** 2hr AUC glucose remained similar from baseline- 4 weeks in the metformin group ($P = 0.83$), whereas it increased in placebo group ($P = 0.01$)
- **Secondary outcome measures:** 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). There was no change in HbA1c in the treatment and placebo groups during the study period ($P = 0.64$). 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 ($P < 0.0001$; $P = 0.003$). 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 ($P = 0.71$). There was 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.

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

STRENGTHS

- Double blinded, randomized, controlled experiment
- No conflicts of interest
- Appropriate inclusion & exclusion criteria
- Specified criteria to meet a power of 90%
- Included number of drop outs and lost to follow up
- Key limitations were mentioned
- Assessed compliance, AE's, & dosage of glucocorticoids after 1 week
- Simplified glucocorticoids to equivalent dose of prednisone
- Appropriate times of measuring data (at baseline, 1 week and at end of study)
- Listed concomitantly taken medications that could have metabolic SE's for each group

LIMITATIONS

- Higher steroid doses in placebo pts, higher baseline A1C in placebo pts
- The way they reported their results & excluded patients in the data analysis
- Their definition of ITT was wrong and they didn't even use ITT like they said they did
- Bad way to measure compliance
- Poor way of defining responders and non-responders
- Duration of study was too short
- Limitations not accounted for appropriately

CONCLUSION

- According to this study, metformin doesn't appear beneficial for metabolic effects with systemic glucocorticoids because there weren't any significant changes in the pertinent metabolic values.
- Future research:
 - The future study needs a larger sample size & longer duration (at least 3 months) with all patients data included or explanation of why it's missing, a better reporting of values, more baseline standardization between patients, metformin that's not near expiration, better assessment of adherence and inclusion of reports of the adherence assessments, and more details on glucocorticoids.

Reference: Seelig E, et. al. Metformin prevents metabolic side effects during systemic glucocorticoid treatment. Eur J Endocrinol. 2017 Mar;176(3):349-358.doi: 10.1530/EJE-16-0653. PubMed PMID: 28073907.

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