1   **Metformin prevents metabolic side effects during systemic glucocorticod treatment**

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27   **ABSTRACT**

28   **Objectives**

29   Patients receiving glucocorticoid treatment are prone to develop metabolic complications. In

30   preclinical studies metformin prevented the development of the metabolic syndrome during

31   glucocorticoid excess. We herein investigated the metabolic effect of metformin during

32   glucocorticoid treatment in non-diabetic patients.

33   **Methods**

34   In a double-blind, placebo-controlled trial, patients starting glucocorticoid treatment

35   (prednisone, prednisolone or methylprednisolone) for four weeks were randomized to

36   concomitantly receive metformin (850mg once daily for one week followed by 850mg twice

37   daily for three weeks) or placebo. All patients underwent a standardized oral glucose

38   tolerance test at baseline and after four weeks. The primary endpoint was change in the 2h

39   area under the curve (AUC) of glucose during the oral glucose tolerance test between baseline

40   and four weeks.

41   **Results**

42   29 of 34 randomized non-diabetic patients completed the trial (17 metformin, 12 placebo). In

43   patients allocated to placebo, median glucose 2h AUC increased from baseline to four weeks

44   (836 [IQR 770-966] to 1202 [1009-1271] mmol l^{-1} min^{-1}; p=0.01). In contrast, glucose levels

45   remained similar to baseline in the metformin group (936 [869-1003] to 912 [825-1011]

46   mmol l^{-1} min^{-1}; p=0.83). This change within four weeks was different between both groups

47   (p=0.005). Glucocorticoid equivalent doses were similar in both groups (placebo: 980.0

48   [560.0-3259.8]mg/28d; metformin: 683.0 [437.5-1970.5]mg/28d; p=0.26).

49   **Conclusions**

50   In this first randomized, controlled trial of metformin targeting metabolic complications in

51   patients needing glucocorticoid therapy, we observed a beneficial effect of metformin on

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52 glycaemic control. Metformin thus seems to be a promising drug for preventing metabolic

53 side   effects   during   systemic   glucocorticoid   treatment.

54   **INTRODUCTION**

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56   Up to 2.5% of the adult western population receive systemic glucocorticoid therapy, mostly

57   for inflammatory conditions. Diabetes mellitus, dyslipidaemia, central obesity and

58   hypertension are well-known and common side effects of glucocorticoid treatment [1, 2].

59   Especially, diabetes mellitus is a recurring problem with a reported prevalence of up to 40%

60   in patients receiving long-term glucocorticoid treatment [3-7]. Even if used as an antiemetic drug

61   in cancer patients, glucocorticoids clearly increased the risk of diabetes mellitus [7]. In contrast

62   to other well-known side effects of glucocorticoids, such as gastric ulcer disease, no

63   randomized-controlled evidence exists that has investigated potential therapeutics for the

64   treatment of metabolic side effects of glucocorticoids.

65

66   Many of the changes seen in glucocorticoid excess, such as gluconeogenesis, correspond to

67   metabolic steps regulated by adenosine-monophosphate-activated protein kinase (AMPK) [8].

68   AMPK is a key regulator of energy metabolism and mediator of several hormones affecting

69   appetite and metabolism [9]. Metformin, a widely used drug for prevention and treatment of

70   diabetes mellitus type 2, exerts most of its beneficial effects on metabolism through the

71   activation of AMPK [10, 11]. We have shown previously that glucocorticoid treatment changes

72   AMPK activity in human adipocytes in vitro and reduced AMPK activity is seen in adipose

73   tissue of patients with Cushing's syndrome [12, 13]. Importantly, metformin reversed the effects

74   of corticosteroids on AMPK in vitro both in primary hypothalamic cell culture as well as in

75   adipocytes, suggesting that metformin and glucocorticoids influence the AMPK signalling

76   pathway in opposite ways and that the metformin effect is able to override the cortisol effect

77   [12, 14]. In vivo studies showed that treatment with an AMPK activator prevented glucocorticoid-

78   induced increase in glucose levels, hepatic glycogen production and hepatic steatosis in rats

79   [15]. Furthermore, metformin efficiently prevented the dexamethasone-induced deterioration of

80   glucose metabolism in mice and horses [16, 17]. These data suggest that metformin treatment

81   could be beneficial in preventing metabolic complications in patients receiving long-term

82   corticosteroid treatment.

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84   In the first double-blind, randomized, placebo-controlled trial we investigated the metabolic

85   effects of metformin during glucocorticoid treatment in non-diabetic patients starting

86   treatment with corticosteroids for at least 4 weeks.

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89   **MATERIALS AND METHODS**

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91   **Study Design**

92   In this randomized, placebo-controlled, double-blind study, we included patients starting

93   glucocorticoid treatment for at least 4 weeks. Participants were recruited at several

94   departments at the University Hospital Basel and the Cantonal Hospital Aarau from August

95   2010 to March 2015. Patients were randomized in a 1:1 ratio to receive either metformin

96   850mg daily p.o. for one week followed by 850mg twice daily p.o. for another three weeks or

97   identical placebo (Merck). The study was terminated after four weeks in all patients, also in

98   cases where glucocorticoid treatment was continued. The study was registered at

99   Clinicaltrials.gov NCT01187849.

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101   **Patients**

102   Inclusion criterion was a newly initiated treatment with prednisone $\geq$7.5mg or an equivalent

103   glucocorticoid for at least 4 weeks. Glucocorticoid tapering was determined by the treating

104   physicians. Exclusion criteria were preexisting diabetes mellitus (according to the American

105   Diabetes Association criteria); renal insufficiency (estimated glomerular filtration rate using

106   the CKD-EPI formula above 60 ml/min/1.73); severe conditions affecting renal function (e.g.

107   dehydration, fever, severe infection); severe conditions causing tissue hypoxia (e.g. acute

108   cardiac or respiratory insufficiency); scheduled examination using intravascular contrast agent

109   containing iodine; alcohol consumption of more than 40g/d (male) or 20g/d (female); known

110   allergy to metformin; pregnancy or breast feeding; any condition compromising the ability of

111   the subject to give written informed consent.

112   The study was approved by the ethical committees of the participating hospitals and

113   Swissmedic and was conducted in accordance with the ethical guidelines of the Declaration of

114   Helsinki. Written informed consent was obtained from all participating subjects before

115   randomization.

116

117   **Study Assessment**

118   At baseline and after four weeks, a standardized 2-hour 75g oral glucose tolerance test was

119   performed. After an overnight fast baseline blood samples for fasting glucose, insulin,

120   HbA1c, a full lipid profile and safety blood measurements were taken directly before

121   ingestion of glucose. Additional blood samples for glucose were taken 30, 60, 90, and 120

122   minutes thereafter.. Physical examination, urine analysis were performed and doses of

123   glucocorticoids were assessed at both visits. After one week, a telephone call took place to

124   assess compliance, adverse events and dosage of glucocorticoids. Three forms of

125   glucocorticoids were prescribed: prednisone, prednisolone and methylprednisolone (Suppl.

126   Tab. 1). If needed, doses of glucocorticoids, e.g. methylprednisolone, were converted to

127   equivalent doses of prednisone [18]. Due to glucocorticoid tapering, cumulative glucocorticoid

128   doses were calculated as follows: area under the curve was calculated using glucocorticoid

129   doses at baseline, one and four weeks. The average daily prednisone dose was calculated as

130   the area under the curve of the 28 study days.

131   Plasma glucose and lipids were measured with enzymatic assays (Cobas® modular analyser,

132   Roche Diagnostics, USA). Serum insulin and c-peptide were assessed using immune assays

133   (Immulite® 2000, Siemens, Germany). Hba1c was analysed in EDTA plasma with high

134   performance liquid chromatography (G8 HPLC Analyzer, Tosho Bioscience, USA).

135   Measurements of all blood parameters were performed in the routine central laboratory unit of

136   the University Hospital Basel. The reported HOMA index was calculated according to

137   Matthews et al. [19]. Body impedance analysis (Bodyimpedance Analyzer Model BIA 101,

138   Akern Srl Florence Italy) was performed to assess body composition and energy expenditure.

139   A randomization list based on single sequence of random assignments, was created by the

140   Pharmaceutical Unit of the University Hospital Basel. Patients as well as study personnel

141   were blinded to the medication allocation.

142

143   **Study End Points**

144   The predefined primary endpoint was the change in the area under the concentration-time

145   curve (AUC) for glucose during the 75g oral glucose tolerance test between baseline and four

146   weeks. Predefined secondary endpoints included change in fasting glucose levels, glycated

147   haemoglobin levels (HbA1c), Homeostatis Model Assessment (HOMA)-Index, fasting lipid

148   levels, body mass index, body composition and waist/hip ratio.

149

150   **Statistical Analysis**

151　According to the protocol, the primary analysis followed the intention to treat principle, i.e.

152　patients with complete follow-up were analysed in the groups to which they were randomized.

153　Patients in the metformin group were expected to have unchanged 2 hour glucose levels after

154　ingestion of 75g glucose, while patients in the placebo group would have an increase of

155　approximately 25%. Based on these assumptions, a sample size of 66 patients (33 per arm)

156　was calculated to detect a significant difference between these distributions with a power of

157　90% at the two-sided 5% level. Discrete variables are expressed as counts (percentages) and

158　continuous variables as median (interquartile range, IQR). To compare changes across

159　treatment groups the Mann-Whitney-U test was used for continuous data and the Fisher's

160　exact test for categorical data. The Wilcoxon signed-rank test was used for comparisons

161　within subjects. Incremental AUC for glucose values (during 120 minutes of a standardized

162　oral glucose tolerance test) and glucocorticoid doses (during 28 days of study duration) was

163　calculated using the trapezoid rule. To adjust for relevant covariates linear regression analyses

164　were employed. P value <0.05 was defined as significant. Data were analysed using statistical

165　software (Statistical Package for Social Sciences, IBM SPSS Version 22, Chicago IL).

166　Figures were drawn using GraphPad Prism (GraphPad Software Inc., LaJolla, CA).

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168

169　**RESULTS**

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171　**Baseline characteristics**

172　34 individuals were randomly assigned (1:1) to receive metformin (n=20) or placebo (n=14).

173　In the metformin group two patients withdrew from the study due to gastrointestinal

174　symptoms and vertigo, respectively; another patient was lost to follow up after the baseline

175　visit. In the placebo group one patient did not receive glucocorticoids as foreseen and one

176   patient was lost to follow up. A total of 17 subjects in the metformin group and 12 subjects in

177   the placebo group completed the trial (Fig. 1). Patients in both treatment groups were well

178   matched for baseline characteristics (Tab. 1). Baseline glucocorticoid doses were similar in

179   both groups (metformin: 35.0 (11.3-50.0) mg/d; placebo: 30.0 (20.0-362.5) mg/d; p=0.48). A

180   comparison between patients completing the trial (n=29) and patients dropping out (n=5)

181   showed no difference in baseline criteria except for glucocorticoid doses (complete: 40.0

182   (20.0-95.0) mg/d; drop out: 12.5 (10.0-26.3) mg/d, p=0.03) (Suppl. Tab. 2). AUC prednisone

183   doses in patients completing the trial remained similar in both groups throughout the study

184   (metformin: 683.0 (437.5-1970.5) mg/28d; placebo: 980.0 (560.0-3259.8) mg/28d, p=0.26).

185   Indications for glucocorticoid treatment are presented in Tab. 2. Concomitant medication

186   with potential effect on glucose and/ or lipid metabolism is listed in Supplemental Table 3.

187   Due to slow study recruitment and time expiry of study drug the study had to be prematurely

188   terminated. This led to fewer study participants than intended and to an unbalanced

189   randomization.

190

191

192   **Effect of Metformin on Glycaemia**

193   2h-AUC glucose remained similar from baseline to four weeks in the metformin group

194   (p=0.83), while increasing in the placebo group (p=0.01; Fig. 2A-C). Accordingly, the

195   primary endpoint of 2h-AUC glucose change within four weeks was different between both

196   groups (p=0.005; Tab 3; Fig. 2D). After adjustment for gender, cumulative glucocorticoid

197   dose and HbA1c, treatment group remained strongly associated with 2h-AUC glucose

198   (adjustment for gender: treatment group p=0.006, R^2=0.32; adjustment for glucocorticoid

199   dose: treatment group p=0.003, R^2=0.33; adjustment for HbA1c: treatment group p=0.002,

200   R^2=0.38). Among the secondary endpoints, the change in fasting glucose, fasting insulin and

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201   HOMA-index were different between the two groups (p=0.01, p=0.003, and p=0.035,

202   respectively; Fig. 3A-F). We observed no change in HbA1c in the treatment and placebo

203   groups during the study period (p=0.64; Fig. 3G-H).

204   Furthermore, we aimed to differentiate between responders and non-responders to metformin.

205   As the 2h AUC glucose increase in the placebo group was 40.3 (18.9-51.0)%, we allocated

206   patients in the metformin group with an increase below 20% to responders, and patients with

207   an increase equal and above 20% to non responders. This resulted in three patients, which

208   were classified as non-responders. Their baseline characteristics are listed in Supplement

209   Table 4.

210   **Effect of Metformin on Lipids**

211   Fasting triglyceride levels did not change during the trial and there was no difference between

212   groups (p=0.30). Total cholesterol levels increased only in the placebo group (p=0.02) while

213   remaining stable in the metformin group (p=0.10). No difference in cholesterol between

214   groups was observed (p=0.15). HDL levels increased in both groups compared to baseline

215   (metformin: p<0.0001; placebo: p=0.003). The HDL increase over the four weeks was more

216   pronounced in the metformin group (p=0.04). LDL levels did not change during the trial and

217   there was no difference between groups (p=0.71; Tab 3).

218

219   **Effect of Metformin on Body Composition and Energy Expenditure**

220   We identified no change in BMI, waist-hip ratio, basal metabolic rate, fat free mass and fat

221   mass during the study period; there was no difference across treatment groups (Tab. 3).

222

223   **Adverse events**

224   Gastrointestinal symptoms were present in 20.0% of patients in the metformin and in 21.4%

225   of patients in the placebo group (Suppl. Tab 5). All gastrointestinal symptoms were either

226   mild or moderate. There was no difference between groups (p=0.99). In the metformin group

227   one subject discontinued the study due to gastrointestinal symptoms, another patient

228   discontinued due to vertigo. One subject in the metformin group was hospitalized for further

229   evaluation of the underlying disease (vasculitis) after study inclusion. The hospitalization was

230   rated as serious adverse event unrelated to the study drug.

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232

233   **DISCUSSION**

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235   In this trial with non-diabetic patients receiving systemic glucocorticoids, we demonstrate for

236   the first time that preventive metformin treatment is superior to placebo with respect to

237   glycaemic control as indicated by 2h glucose AUC, HOMA-Index, fasting glucose and fasting

238   insulin. This effect was consistent after adjustment for gender, cumulative glucocorticoid dose

239   and HbA1c. While HDL cholesterol levels increased in both groups during GC treatment, we

240   did not observe a change in triglycerides, LDL, body weight or body composition.

241

242   Despite the very frequent use of glucocorticoids and the well-known detrimental impact on

243   glucose metabolism, hardly any randomized-controlled trials have investigated the prevention

244   of glucocorticoid-induced diabetes [20-23]. In one of these trials, troglitazone prevented

245   deterioration of glucose metabolism during glucocorticoid treatment, while pioglitazone and

246   metformin had no effect [24]. Noteworthy, troglitazone can no longer be used as it was

247   withdrawn from the market. Compared to our study, duration of metformin and steroid

248   treatment was very short and metformin dose was low. Two other randomized controlled

249   trials targeting the GLP-1 pathway produced heterogenous results [25, 26]. Importantly, all three

250   studies were performed in individuals without inflammatory disease, thus not representing the

251   patients in need of glucocorticoid treatment. As inflammation is a known mediator of insulin

252   resistance, it is important to investigate potential benefits of metformin in an appropriate

253   study population [27]. Therefore, more convincing strategies to prevent metabolic side effects of

254   glucocorticoid treatment in patients indeed suffering from inflammatory diseases are needed.

255   From a pathophysiological point of view, metformin is an attractive preventive treatment

256   strategy in patients receiving corticosteroids. Metformin's mode of function has been

257   extensively discussed and several mechanisms such as inhibition of glycerolphosphate

258   dehydrogenase, enhanced action of glucagon-like-peptide 1 or antagonism of glucagon have

259   been proposed [28-31]. Overall, activation of AMPK seems to play an important role [10, 11, 32, 33].

260   AMPK is generally considered to be a master regulator of energy metabolism, sensing energy

261   depletion and activating energy-generating pathways [9]. Glucocorticoids have been shown to

262   inhibit AMPK activity and, importantly, metformin was able to reverse this inhibitory effect

263   of glucocorticoids on AMPK in vitro and in animal studies [12, 13, 15].

264   In accordance with these experimental data, our study showed that metformin favourably

265   influences several side effects of glucocorticoid therapy. We found that metformin prevented

266   an increase of 2h glucose AUC indicating preservation of glucose tolerance. The HOMA-

267   Index, a marker of insulin resistance, clearly improved in the metformin group while

268   deterioration was observed in the placebo group. Fasting glucose levels decreased in the

269   metformin group while increasing in the placebo group during the study period. Moreover,

270   change in fasting insulin was different between groups. Still, we could not identify a

271   difference in HbA1c. However, our study was conducted over four weeks while HbA1c

272   reflects average blood glucose over the previous 8 to 12 weeks [34]. Therefore, we speculate

273   that a longer study duration could show a beneficial effect on HbA1c.

274   Compared to glucose metabolism, the role of glucocorticoids in lipid metabolism is more

275   controversial. Patients with endogenous overproduction of glucocorticoids are prone to

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276   develop dyslipidaemia [1]. Similarly, glucocorticoid administration has been associated with

277   deterioration of lipid metabolism [35]. Interestingly, in a large observational study,

278   glucocorticoids were associated with higher HDL levels and glucocorticoid treatment was

279   shown to normalize HDL levels in rheumatoid arthritis [36-38]. This positive effect of

280   glucocorticoids may be due to the reduction of the inflammatory burden rather than a direct

281   impact on lipid metabolism.

282   While the role of glucocorticoids on lipids remains unclear, metformin presumably has a

283   beneficial effect by decreasing triglycerides and LDL cholesterol while increasing HDL

284   cholesterol independent of glucose metabolism [39-41]. In our trial, we did not observe a change

285   in triglycerides nor LDL; however, HDL cholesterol levels increased in both study groups.

286   This finding may be due to a direct effect of glucocorticoids or rather an indirect effect of

287   lowering the inflammatory status.

288   Central obesity is another characteristic feature of chronic high dose glucocorticoid exposure

289   [42, 43]. In the Diabetes Prevention Program Study metformin reduced body weight for around

290   2kg during a two year study period in diabetic patients [44]. Thus, metformin exerts opposite

291   effects to glucocorticoids regarding weight.

292   In our trial, four weeks of glucocorticoid treatment did not result in change of body

293   composition or waist/hip ratio in either study groups. Consequently, no effect of metformin

294   could be observed. Possibly, the study duration was too short and the sample size too small;

295   longer treatment duration with corticosteroids and metformin or placebo, respectively, may

296   provide different results.

297

298   Gastrointestinal adverse events occurred in similar number in both treatment groups. Several

299   other studies found metformin to be safe and well tolerated [45].

300

301   Our study has some limitations. First, the study was prematurely terminated which led to a

302   rather small sample size. This was due to a combination of slow and difficult recruitment and

303   time to expiry of the trial drug. Nevertheless, due to higher than expected effect of metformin

304   the sample size was sufficient to demonstrate a significant effect on the primary and several

305   secondary endpoints. Since we show a highly significant result, lack of statistical power is not

306   an issue. Second, more and predominantly male patients were in the metformin group. Third,

307   causes of glucocorticoid administration were very variable and the study design did not allow

308   stratification of diseases. While overall glucocorticoid doses were not different between

309   groups, some participants in the placebo group received the highest doses. Importantly,

310   variability of indications and administration of glucocorticoid treatment mirror real life

311   practice, and make the results more generalizable. Fourth, baseline HbA1c was slightly higher

312   in the placebo group, potentially putting these patients at higher risk for development of

313   diabetes. Importantly, the difference in HbA1c was not significant between groups, and the

314   primary endpoint remained highly significant after adjustment for HbA1c.

315   Our results indicate that metformin prevents deterioration of glucose metabolism if treatment

316   is timed with initiation of glucocorticoids. This study provides the basis for metformin as a

317   preventive treatment in patients newly receiving glucocorticoid therapy. Further studies are

318   needed to test if occurrence of glucocorticoid-induced diabetes can be reduced, and if

319   metformin has similar beneficial effects in patients with continuous glucocorticoid treatment.

320   As our patient number was too small to identify unique characteristics distinguishing

321   responders from non-responders, this remains to be investigated in future studies.

322   In summary, this is the first randomized-controlled trial showing that metformin has a

323   beneficial preventive effect on glycaemic control in non-diabetic patients receiving systemic

324   glucocorticoid therapy.

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326 **DECLARATION OF INTEREST**

327 All authors declare no conflict of interest.

328

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331

332

333 **AUTHOR CONTRIBUTIONS**

334 M.C.-C. designed the study. E.S., S.M., T.K. N.N., M.B. conducted the experiments. E.S.

335 analysed the data. E.S., S.M., M.C.-C. wrote the manuscript. T.K., I.P., P.S., B.M., M.K.

336 reviewed and edited the manuscript. M.C.-C. is the guarantor of the study and, as such, takes

337 responsibility for the contents of this article.

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497   **FIGURE LEGENDS**

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499   Fig. 1. Enrolment of participants

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501   Fig. 2. Change in glucose during oral glucose tolerance test

502   A) Plasma glucose values during oral glucose tolerance test at baseline and after four weeks in

503   placebo treated patients. B) Glucose values during oral glucose tolerance test at baseline and

504   after four weeks in patients treated with metformin. C) 2h-AUC glucose in both study groups

505   at baseline and after 4 weeks. D) Differences in 2h-AUC glucose between baseline and four

506   weeks in each study group. Data represent median values error bars indicate interquartile

507   ranges. * indicates p-value <0.05.

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509   Fig. 3. Change in HOMA-Index, fasting glucose, fasting insulin and HbA1c

510   A) HOMA-Index at baseline and after four weeks for both study groups. B) Differences in

511   HOMA-Index between baseline and four weeks in each study group. C) Fasting glucose at

512   baseline and after four weeks in each study group. D) Differences in fasting glucose between

513   baseline and four weeks in each study group. E) Fasting insulin at baseline and after four

514   weeks in each study group. F) Differences in fasting insulin at baseline and after four weeks

515   in each study group. G) HbA1c at baseline and after four weeks in each study group. H)

516   Differences in between baseline and four weeks in each study group. Data represent median

517   values, error bars indicate interquartile ranges. * indicates p-value <0.05.

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Tab. 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 2h AUC (mmol l^{-1} min^{-1})	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/d)	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

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Fat mass (kg)	16.9 (9.3-22.1)	14.6 (8.5-21.2)	0.77

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Tab. 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 erythematodes	1	
Sarcoidosis		2
Sclerosing Lymphadenopathy	1	
Cutaneous sclerosis		1
MorbusWegener	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

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Tab. 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 ([a] Prednisone dosage was calculated as area under the curve using glucocorticoid doses at baseline, one and four weeks).

	Placebo	Metformin	Between-group p
Glucose 2h AUC (mmol l^{-1} min^{-1}; 17 patients on metformin vs. 8 on placebo)			
Baseline	835.5 (769.9-966.0)	936.0 (869.3-1002.8)	0.005
4 weeks	1202.3 (1008.8-1270.9)	912.0 (825.0-1011.0)	
Within-group p	0.01	0.83	
HOMA-Index (17 vs. 9)			
Baseline	1.0 (0.4-1.4)	2.2 (1.0-3.6)	0.035
4 weeks	1.5 (0.8-2.0)	1.1 (0.6-2.7)	
Within-group p	0.07	0.04	
Fasting glucose (mmol/l; 17 vs. 11)			
Baseline	4.8 (4.4-5.3)	4.8 (4.6-5.3)	0.01

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4 weeks	5.3 (4.5-5.6)	4.6 (4.2-5.0)	
Within-group p	0.07	0.04	
Insulin (mIU/L; 17 vs. 10)			
Baseline	5.4 (2.3-8.3)	9.3 (4.5-15.6)	0.003
4 weeks	6.8 (4.0-13.4)	5.7 (3.3-13.4)	
Within-group p	0.07	0.06	
HbA1c (%; 16 vs.12)			
Baseline	5.7 (5.3-5.9)	5.4 (5.3-6.0)	0.64
4 weeks	5.8 (5.3-5.9)	5.5 (5.3-6.0)	
Within-group p	0.19	0.48	
HbA1c (mmol/mol; 16 vs. 12)			
Baseline	39.0 (34.0-41.0)	36.0 (34.0-42.0)	0.64
4 weeks	40.0 (34.0-41.0)	37.0 (34.0-42.0)	
Within-group p	0.19	0.48	
Triglycerides (mmol/l; 17 vs. 11)			
Baseline	1.1 (0.8-1.1)	1.3 (0.9-1.6)	0.30
4 weeks	1.2 (0.9-1.3)	1.2 (1.0-1.4)	
Within-group p	0.17	0.65	
Total cholesterol (mmol/l; 17 vs. 11)			
Baseline	4.8 (4.5-5.1)	4.8 (4.2-5.7)	0.15
4 weeks	5.6 (4.8-6.9)	5.4 (4.6-6.4)	

Within-group p	0.02	0.10	
HDL (mmol/l; 17 vs. 11)			
Baseline	1.5 (1.0-1.6)	1.3 (1.1-1.5)	0.04
4 weeks	2.0 (1.7-2.8)	1.7 (1.3-1.9)	
Within-group p	0.003	<0.0001	
LDL (mmol/l; 17 vs. 11)			
Baseline	2.9 (2.6-3.1)	3.0 (2.3-3.9)	0.71
4 weeks	3.0 (2.7-3.4)	3.0 (2.5-3.8)	
Within-group p	0.53	0.83	
BMI (kg/m^2; 17 vs. 12)			
Baseline	25.7 (21.9-26.4)	23.7 (20.9-28.7)	0.30
4 weeks	25.5 (21.4-27.4)	23.6 (21.1-28.7)	
Within-group p	0.72	0.26	
Waist-hip ratio (16 vs. 9)			
Baseline	0.9 (0.8-1.0)	1.0 (0.9-1.0)	0.36
4 weeks	1.0 (0.9-1.0)	1.0 (0.9-1.0)	
Within-group p	0.17	0.93	
Basal metabolic rate (kcal; 14 vs. 10)			
Baseline	1665 (1523-1888)	1730 (1550-1835)	0.95

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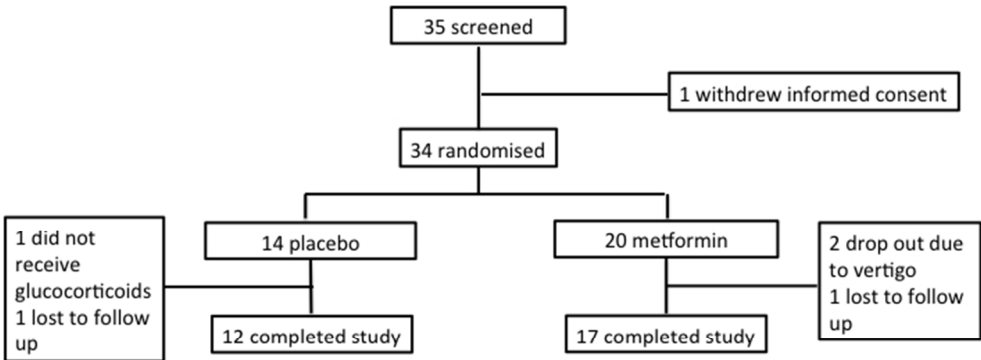|			
4 weeks	1620 (1418-1952)	1745 (1513-1820)	
Within-group p	0.65	0.55	
Fat free mass (kg; 14 vs. 10)			
Baseline	57.0 (47.5-62.3)	58.3 (52.9-63.9)	0.38
4 weeks	54.7 (41.6-63.2)	57.7 (51.5-64.7)	
Within-group p	0.37	0.95	
Fat mass (kg; 14 vs. 10)			
Baseline	16.9 (10.4-21.3)	14.6 (9.8-22.3)	0.98
4 weeks	19.2 (12.1-22.8)	17.1 (9.5-22.9)	
Within-group p	0.59	0.35	
AUC Prednisone dosage (mg/28d: 17 vs 12) [a]	980.0 (560.0-3259.8)	683.0 (437.5-1970.5)	0.26

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Fig 1)

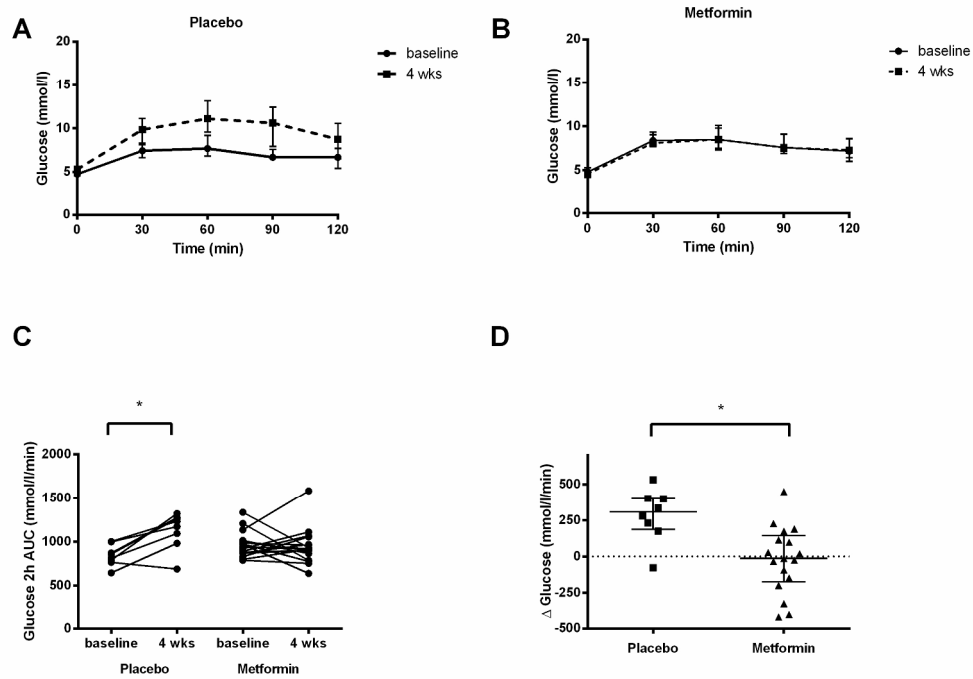Fig. 1. Enrolment of participants

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Fig. 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) 2h-AUC glucose in both study groups at baseline and after 4 weeks. D) Differences in 2h-AUC glucose between baseline and four weeks in each study group. Data represent median values error bars indicate interquartile ranges. * indicates p-value <0.05.
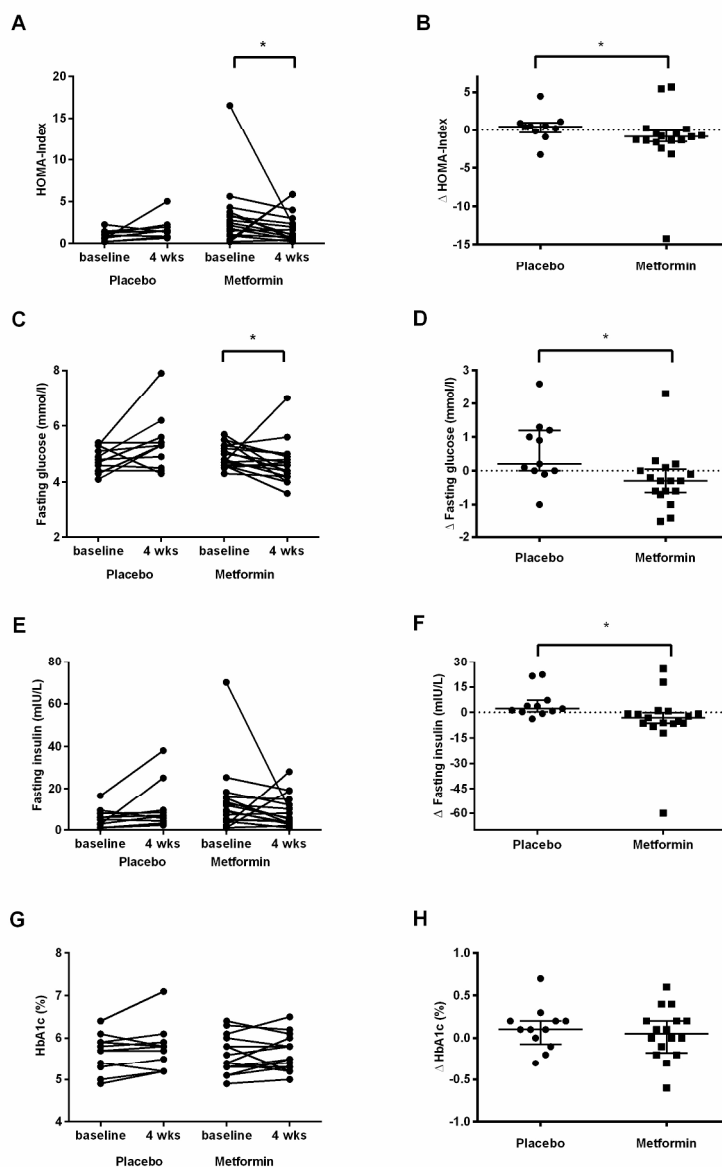
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Fig. 3. Change in HOMA-Index, fasting glucose, fasting insulin and HbA1c
A) HOMA-Index at baseline and after four weeks for both study groups. B) Differences in HOMA-Index between baseline and four weeks in each study group. C) Fasting glucose at baseline 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. * indicates p-value <0.05.

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