Pioglitazone improves insulin resistance and decreases blood pressure in adult patients with congenital adrenal hyperplasia

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Abstract

Context: Patients with congenital adrenal hyperplasia (CAH) are chronically treated with supraphysiological doses of glucocorticoids, which are known to induce insulin resistance. Thiazolidinediones might reverse this effect and improve insulin sensitivity.

Objectives: To assess insulin sensitivity in CAH patients and the effect of pioglitazone treatment on insulin sensitivity in CAH patients. Secondary objectives were the effects of treatment with pioglitazone on blood pressure, body fat distribution, lipid, and steroid profiles.

Design: Randomized placebo controlled crossover trial.

Participants: Twelve CAH patients and 12 body mass and age-matched control subjects.

Intervention: Sixteen-week treatment with pioglitazone (45 mg/day) or placebo.

Main outcome measure: Insulin sensitivity measured by euglycemic clamp and oral glucose tolerance test. Further measures were 24-h blood pressure profiles, body fat distribution measured by magnetic resonance imaging, dual energy x-ray absorptiometry (DEXA) and bioimpedance procedures, liver fat by magnetic resonance spectroscopy, lipid, and steroid profiles.

Results: CAH patients were insulin resistant compared with healthy controls. Treatment with pioglitazone significantly improved insulin sensitivity in CAH patients (glucose infusion rate (GIR) from 28.5 ± 11.6 to 38.9 ± 11.0 μmol/kg per min, P < 0.001, GIR in controls 46.2 ± 23.4 μmol/kg per min. P < 0.05 versus CAH). Treatment with pioglitazone decreased blood pressure (systolic: 124.0 ± 13.6 vs 127.0 ± 14.9 mmHg, P < 0.001, diastolic: 72.8 ± 11.5 vs 77.4 ± 12.6 mmHg, P < 0.001). No changes in body fat distribution, lipid, and steroid profiles were observed.

Conclusions: CAH patients are insulin resistant compared with matched control subjects. Treatment with pioglitazone improves insulin sensitivity and decreases blood pressure in CAH patients.

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition, which is in more than 95% of the cases caused by a mutation in the gene for 21-hydroxylase (1). This defect results in increased secretion of ACTH, adrenal hyperplasia and increased production of androgens, but glucocorticoid deficiency. Current treatment comprises glucocorticoid (and, if necessary, mineralocorticoid) administration to prevent adrenal crises and suppress the abnormal secretion of androgens. However, because glucocorticoids are given in slightly supraphysiological doses and the therapeutic range for glucocorticoids is narrow, patients are at risk of developing iatrogenic Cushing’s syndrome (1).

Glucocorticoids induce insulin resistance in humans (2), and may precipitate diabetes in susceptible subjects. Chronic exogenous or endogenous oversupply with glucocorticoids is associated with changes in fat distribution, typically toward more central/visceral fat. Whether the observed insulin resistance is related to these changes in body fat distribution is not known.

The use of supraphysiological doses of glucocorticoids and androgen excess in CAH patients are associated with the development of an unfavorable cardiovascular risk profile (3). Data on the prevalence of cardiovascular morbidity or life expectancy in CAH patients are not yet available. In this respect, it is of interest that a recent population-based study in Sweden has showed that patients with Addison’s disease have a clearly increased mortality rate. The excess mortality in both males and females was for a major part caused by cardiovascular disease. The authors of this study suggested that the increased cardiovascular mortality in Addison’s patients is caused by excess glucocorticoid exposure (4).

Of the few studies that have explored insulin sensitivity in CAH, most have concluded that CAH patients are indeed characterized by insulin resistance...
CAH patients are characterized by insulin resistance and have an unfavorable cardiovascular risk profile, so it might be a rational option to improve their insulin sensitivity with insulin sensitizers. Improving their cardiovascular risk profile might also improve their life expectancy. Thiazolidinediones (TZDs) improve insulin sensitivity in several conditions associated with insulin resistance. The improvement of insulin sensitivity is associated with beneficial changes in several parameters, like lipids, blood pressure, and vascular function, and changes in inflammatory markers (14, 15). Therefore, TZDs might be a rational therapeutic option in glucocorticoid-induced insulin resistance, as has been suggested by earlier studies (16, 17). Such improvement in insulin sensitivity might have a twofold benefit: first, glucose tolerance in patients with limited β-cell function will improve and hence the chance to develop overt type 2 diabetes will decrease. Secondly, cardiovascular risk factors associated with insulin resistance will improve (18).

In the present study, we tested the hypotheses that CAH patients who are chronically treated with glucocorticoids are insulin resistant and that treatment with pioglitazone improves insulin sensitivity in this group. Insulin sensitivity was assessed using the euglycemic clamp procedure. We also measured the effect of pioglitazone treatment on body fat distribution, including liver fat content, blood pressure, and lipid profile.

Materials and methods

Patients

Adult subjects with biochemically and genetically proven CAH on a stable corticosteroid replacement dose for 3 months were included in the study. Characteristics of the study population are shown in Table 1. Gender, phenotype, results of mutation analysis, medication, and mean salivary androstenedione levels of the study population are shown in Table 2. Exclusion criteria were as follows: age <18 years, inability to give informed consent, significant cardiovascular disease (defined as myocardial infarction or stroke 6 months preceding the study), significant renal disease (defined as a glomerular filtration rate (GFR) <30 ml/min), significant liver disease (defined as alanine aminotransferase and aspartate aminotransferase levels of more than three times the upper limit of normal), and mental disease. All patients were fully informed about the aim and design of the study and all the methods involved. They consented with the study protocol which was approved by the institutional review board of the Radboud University Nijmegen Medical Centre.

Insulin sensitivity in CAH patients treated with glucocorticoids was compared to insulin sensitivity measured in a group of body mass index (BMI) and age-matched normal subjects. These subjects were selected in a case–control design from a larger cohort earlier described (19). Characteristics of the control group are shown in Table 1.

Methods

At screening, all patients underwent a full physical examination and electrocardiography. Blood was drawn for determination of liver function and renal function. To estimate GFR, the MDRD–GFR equation was used (20). After a 4-week run-in phase, patients were randomized to treatment with either placebo for 16 weeks, followed by pioglitazone (45 mg/day) for 16 weeks, or treatment with pioglitazone for 16 weeks, followed by placebo for 16 weeks in a randomized crossover design. Patients visited the clinic every 2 months for medication checks, adverse events, and measurement of weight, blood pressure, and edema formation. Safety measures included assessment of weight, blood pressure, and edema. At the end of the respective study periods, fasting glucose, lipid, and hormone levels (insulin, ACTH, cortisol, aldosterone, renin, 17-OH progesterone and androstenedione in serum, and 17-OH progesterone and androstenedione in saliva in the morning, afternoon, and evening) were assessed and insulin sensitivity was measured using a euglycemic hyperinsulinemic (steady-state plasma insulin level
<table>
<thead>
<tr>
<th>P</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Phenotype</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>BMI (kg/m²)</th>
<th>Daily glucocorticoid therapy</th>
<th>Daily mineralocorticoid therapy</th>
<th>Mean salivary androstenedione levels (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>F</td>
<td>Nonclassical</td>
<td>c.841G&gt;T (p.Val281Leu)</td>
<td>c.841G&gt;T (p.Val281Leu)</td>
<td>19.2</td>
<td>HC: 20–5 mg (0800–2300 h)</td>
<td>–</td>
<td>0.07</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>F</td>
<td>SW</td>
<td>del/conv</td>
<td>del/conv</td>
<td>37.6</td>
<td>HC: 25–10 mg (0900–1700 h)</td>
<td>0.1 mg</td>
<td>0.08</td>
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<tr>
<td>3</td>
<td>33</td>
<td>M</td>
<td>SW</td>
<td>del/conv</td>
<td>del/conv</td>
<td>29.9</td>
<td>HC: 15–5–7.5 mg (9.00 am – 0.30 pm – 11.30 pm)</td>
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<tr>
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<td>52</td>
<td>M</td>
<td>SV</td>
<td>c.515T&gt;A (p.Ile172Asn)</td>
<td>del/conv</td>
<td>29.6</td>
<td>HC: 17.5–10 mg (0730–1830 h)</td>
<td>–</td>
<td>0.83</td>
</tr>
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<td>5</td>
<td>45</td>
<td>M</td>
<td>SV</td>
<td>c.290-13A/C&gt;G</td>
<td>del/conv</td>
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<td>HC: 10–10 mg (0800–2300 h)</td>
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<td>0.14</td>
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<td>F</td>
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<td>25.7</td>
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<td>c.290-13A/C&gt;G</td>
<td>c.329-336del (p.Gly110fs)</td>
<td>23.4</td>
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<td>0.18</td>
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<td>8</td>
<td>42</td>
<td>F</td>
<td>SW</td>
<td>c.290-13A/C&gt;G</td>
<td>c.952C&gt;T (p.Gln318X)</td>
<td>29.5</td>
<td>HC: 17.5–15 mg (every other day, 0630–1730 h)</td>
<td>0.150 mg</td>
<td>0.17</td>
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<td>9</td>
<td>28</td>
<td>F</td>
<td>SW</td>
<td>c.1066C&gt;T (p.Arg356Trp)</td>
<td>c.1066C&gt;T (p.Arg356Trp)</td>
<td>24.5</td>
<td>HC: 10–10 mg (0800–2230 h)</td>
<td>0.0625–0.125 mg (every other day)</td>
<td>0.03</td>
</tr>
<tr>
<td>10</td>
<td>28</td>
<td>M</td>
<td>SW</td>
<td>del/conv</td>
<td>del/conv</td>
<td>23.6</td>
<td>HC: 10–15 mg (0500–0900 h), DXM: 0.25 mg (ante noctem)</td>
<td>0.4 mg</td>
<td>0.08</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
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<td>del/conv</td>
<td>c.515T&gt;A (p.Ile172Asn)</td>
<td>24.4</td>
<td>HC: 15–5 mg (0830–2330 h)</td>
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<td>0.50</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>F</td>
<td>SW</td>
<td>c.707T&gt;A (p.Ile236Asn), c.710T&gt;A (p.Val237Glu), c.716T&gt;A (p.Met239Lys)</td>
<td>del/conv</td>
<td>29.5</td>
<td>DXM: 0.1–0.1 mg (0730–2300 h)</td>
<td>0.3 mg</td>
<td>0.44</td>
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</tbody>
</table>

P, patient number; F, female; M, male; del, deletion; conv, conversion; HC, hydrocortisone; DXM, dexamethasone.

SW, classic salt wasting CAH; SV, classic simple virilizing CAH.

Nucleotides are numbered according to the HGVS guidelines using Genbank entry NM_000500.5 as reference sequence, where the A of the first ATG is 1. The variable leucine stretch in exon 1 was counted as 4, not 5 leucines to comply with the widely accepted numbering used in the literature.

Mineralocorticoid medication (9α-fluorohydrocortisone acetate) was taken in one to two doses.

Salivary levels of androstenedione are mean levels from six samples (see Materials and methods).
~ 600 pmol/l) clamp. Glucose tolerance was measured using an oral 75-g glucose load. Blood glucose and insulin samples were collected at 30, 60, 90, and 120 min after the test load. Glucose tolerance was evaluated using the criteria of WHO (21). Body fat distribution was assessed by two different methods, magnetic resonance imaging (MRI) and DEXA scanning. Total body DEXA scanning was performed using a Hologic QDR 4500 densitometer (Hologic, Bedford, MA, USA) to determine total bone mineral content (BMC, g), total areal bone mineral density (g/cm²), fat mass, and lean mass. Twenty-four-hour ambulatory blood pressure measurement was performed using the ambulatory SpaceLabs model 90207 blood pressure monitoring system. Mean salivary androstenedione levels were calculated from six samples: three samples after placebo treatment and three samples after pioglitazone treatment (same time points as after placebo treatment). Undertreatment was defined as the presence of a mean level of salivary androstenedione above the upper reference morning (0800 h) level, i.e. more than 0.63 nmol/l in males and 1.1 nmol/l in females. Overtreatment was defined as the presence of a mean level of salivary androstenedione below the lower reference morning (0800 h) level, i.e. lower than 0.14 nmol/l in males and 0.16 nmol/l in females.

In control subjects insulin sensitivity was measured using the same euglycemic hyperinsulinemic clamp procedure as in CAH patients.

**Procedures**

**Euglycemic clamp** Experiments were performed in the morning after an overnight (10 h) fast. Two i.v. cannulae were inserted. One positioned retrogradely into a dorsal vein of the hand that was placed in a Plexiglas box, ventilated with heated air, for sampling of arterialized venous blood (22). The second cannula was inserted in an antecubital vein of the contralateral arm for infusion of insulin and glucose. Insulin (Actrapid, NovoNordisk, Bagsvaerd, Denmark; diluted in NaCl of 0.9% to a concentration of 1 U/ml, with the addition of 2 ml whole blood per 50 ml) was infused at a rate of 60 mU/min per m² body surface area (360 pmol/min per m²). Arterialized venous plasma glucose was measured in duplicate at 5-min intervals by the glucose oxidation method (Beckman Glucose Analyser II, Beckman, Fullerton, CA, USA). Plasma glucose was clamped at the fasting level by a variable infusion of glucose 20% solution. Plasma insulin was measured in all samples with an in-house RIA at the start of the clamp procedure and after 90 and 120 min (23). Whole body glucose disposal was determined by glucose infusion rate (GIR) as: (mean glucose infusion 90–120 min (mg/min)/weight (kg)) × (1000/180 g/mol) µmol/min per kg.

**Magnetic resonance imaging and spectroscopy** Liver fat content and abdominal fat distribution were determined by proton magnetic resonance spectroscopy (MRS) and imaging (MRI) on a clinical 3T whole body MR system (Siemens Magnetom Tim Trio, Erlangen, Germany). All measurements were carried out during breath-holding for 15 s. Liver fat content was determined by single-voxel proton MR spectra with STEAM localization (echo time 20 ms; repetition time 3 s). Hepatic fat percentage was calculated without correction for differences in relaxation times by dividing the lipid methylene signal intensity at 1.3 ppm by the sum of the methylene lipid and water signal intensities and multiplying the result by 100. Abdominal fat distribution was derived from 16 T1-weighted FLASH-2D axial MR images from a region extending from 4 cm above to 4 cm below the fourth and fifth lumbar interspaces. Subcutaneous and visceral fat volumes were determined based on signal intensity.

**Statistical analysis**

For calculation and statistical analyses, the SPSS personal computer software package was used (SPSS Inc., Chicago, IL, USA) and P < 0.05 was considered statistically significant. Differences between pioglitazone and placebo were statistically tested using Student’s t-test or the Wilcoxon–Mann–Whitney test as appropriate. According to power calculations, detecting a 20% change in insulin sensitivity with a power of 80% at a significance level of 0.05 would require 11 subjects completing the study.

**Results**

A total of 12 CAH patients completed the study, seven females and five males. All patients had a biochemically and genetically proven CAH and were treated with stable corticosteroid doses for at least 3 months. Eight patients had the classic salt wasting type of CAH, three patients had the classic simple virilizing type of CAH and one patient had a nonclassical type of CAH. Evaluation of mean salivary androstenedione levels showed that six patients were adequately treated, five patients were overtreated and one patient was undertreated (data shown in Table 2).

**Insulin sensitivity**

CAH patients were insulin resistant compared with the control group using the euglycemic clamp procedure (GIR 28.5 ± 11.6 vs 46.2 ± 23.4 µmol/kg per min, CAH patients versus controls respectively, P = 0.04, Fig. 1). Similarly, the insulin sensitivity index in CAH patients was significantly lower compared with control subjects (0.35 ± 0.16 vs 0.56 ± 0.30 µmol/kg per min (mU/l), P = 0.03).
subcutaneous fat ratio, and the percentage of liver fat after the use of pioglitazone compared to placebo (Table 3). Most patients had relatively low amounts of liver fat. The only patients with a high liver fat content during placebo (32.7%) showed a strong decrease in the percentage of liver fat after the use of pioglitazone (19.3%). Other patients did not show a decrease in the percentage of liver fat after the use of pioglitazone.

DEXA scanning showed no relevant changes in total body BMC, total lean mass, total fat mass, lean and fat mass in trunk, arms, and legs, and the distribution of the fat mass after use of placebo or pioglitazone compared to baseline data.

**Blood pressure profiles**

Ambulatory 24-h blood pressure was significantly lower during pioglitazone compared with placebo treatment (systolic: 124.0 ± 13.6 vs 127.0 ± 14.9 mmHg, \(P<0.001\), diastolic: 72.8 ± 11.5 vs 77.4 ± 12.6 mmHg, \(P<0.001\), Fig. 2 and Table 4).

**Clinical characteristics, lipid profile, and steroid profile**

Clinical characteristics, like weight, BMI, waist, hip, and waist/hip ratio were not significantly different after the use of placebo or pioglitazone. No significant changes in lipid profile and levels of steroids, ACTH, and renin were observed after the use of pioglitazone compared to placebo.

**Discussion**

The main findings of the present study are that CAH patients who are chronically treated with glucocorticoids are insulin resistant as compared with body mass and age-matched normal subjects and that treatment with pioglitazone improves insulin sensitivity in this group of patients.

The finding that CAH is associated with insulin resistance is in line with earlier studies. These prior studies suggest that both overproduction of androgens and treatment with (supraphysiological doses of) glucocorticoids can induce insulin resistance (5–11, 26, 27).

In our study, we document a significantly lower insulin sensitivity index and GIR in adult CAH patients who were chronically treated with glucocorticoids. The observed insulin resistance may well be the result of treatment with glucocorticoids. Glucocorticoids are known to induce insulin resistance, although the mechanisms involved are incompletely understood (28). Supraphysiological doses of glucocorticoids also increase lipolysis and plasma free fatty acids (FFA), which may lead to insulin resistance in muscles (16, 29).

Insulin resistance is known to be a risk factor for the development of cardiovascular disease and to precede
the development of type 2 diabetes (30, 31). Therefore, CAH patients might be at risk to develop type 2 diabetes or cardiovascular disease later in life. Because CAH patients need to continue glucocorticoid treatment to suppress overproduction of androgens and as substitution of cortisol, we reasoned that an intervention with insulin-sensitizing drugs, like TZDs, might have a favorable effect on insulin sensitivity in CAH patients and as a result improve their cardiovascular risk profile (15).

We observed a significant improvement of insulin sensitivity (measured both by clamp and by insulin response during OGTT) in CAH patients treated with pioglitazone, although not to the level of the healthy control group. Pioglitazone is known for its ability to improve insulin sensitivity in several conditions associated with insulin resistance. It has been hypothesized that TZDs have an insulin-sensitizing effect because of alterations in adipokine release, which modulates insulin sensitivity outside adipose tissue (15). TZDs also promote the uptake and the storage of fatty acids in adipose tissue, which does lead to an increase in adipose tissue mass, but in this way TZDs spare other insulin-sensitive tissues as the liver and the skeletal muscle form the harmful metabolic effect of high concentrations of FFA (15).

During pioglitazone treatment, ambulatory 24-h systolic and diastolic blood pressures decreased significantly. It has been noticed before that TZDs can improve blood pressure profiles, although the exact mechanism is not yet known. Insulin resistance is known to be a risk factor for the development of hypertension, so one may hypothesize that improvement of insulin sensitivity may also decrease blood pressure. Insulin resistance contributes to the development of hypertension through several mechanisms like angiotensin II and aldosterone actions, enhanced sympathetic nervous system activity, dyslipidemia, atherosclerosis, left ventricular hypertrophy and changes in renal function and structure, like glomerulosclerosis (32). The anti-hypertensive effects of pioglitazone have been studied in Japanese male patients with type 2 diabetes (33). This study showed a significant decrease in mean blood pressure (109 ± 14 to 101 ± 10 mmHg) after 3 months of treatment with pioglitazone (30 mg/day). Results of the present study are in line with these findings. Anti-hypertensive effects of pioglitazone have also been described in type 2 diabetics with difficult-to-control hypertension, nondipping diabetic patients, and in diet-induced obese rats (34–36).

Although our study shows favorable effects of pioglitazone on insulin sensitivity and blood pressure in adult CAH patients, it has become uncertain whether pioglitazone is a valuable addition to current treatment strategies. Recent studies have questioned the long-term safety of TZDs, especially with respect to long-term cardiovascular outcome. Frequently noticed side effects of TZDs include edema, weight gain, macular edema, and heart failure. Furthermore, TZDs tend to increase low-density lipoprotein cholesterol levels (37). Rosiglitazone may even be associated with a higher risk of myocardial infarction and death due to cardiovascular causes (38), but the RECORD study only confirmed the increased risk of heart failure (39). The PROActive Study showed favorable effects of pioglitazone on reduction of all-cause mortality, nonfatal myocardial infarction, and stroke in type 2 diabetes patients (40). Longer follow-up of treatment with TZDs is needed to evaluate their effects on congestive heart failure and cardiovascular death (41). Treatment with TZDs also decreases bone formation and bone mass, possibly as a result of promoting adipogenesis above osteoblastogenesis (42). This side effect seems particularly relevant in our group of patients, against the background of the already ongoing adverse effect of corticosteroids on the bone. Over this short treatment period, we did not observe any

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Table 4 Twenty-four-hour ambulatory blood pressure during pioglitazone or placebo treatment in congenital adrenal hyperplasia patients.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Pioglitazone</th>
<th><em>P</em> value</th>
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</thead>
<tbody>
<tr>
<td>24-h SBP</td>
<td>127.0±14.9</td>
<td>124.0±13.6</td>
<td>0.000</td>
</tr>
<tr>
<td>24-h DBP</td>
<td>77.4±12.6</td>
<td>72.8±11.5</td>
<td>0.000</td>
</tr>
<tr>
<td>24-h HR</td>
<td>77.1±13.9</td>
<td>75.1±13.5</td>
<td>0.007</td>
</tr>
<tr>
<td>24-h MAP</td>
<td>93.4±12.5</td>
<td>89.4±11.1</td>
<td>0.000</td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>129.9±13.4</td>
<td>127.7±12.1</td>
<td>0.017</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td>79.9±11.5</td>
<td>75.3±11.0</td>
<td>0.000</td>
</tr>
<tr>
<td>Daytime HR</td>
<td>78.9±12.9</td>
<td>78.1±12.9</td>
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</tr>
<tr>
<td>Daytime MAP</td>
<td>95.9±11.3</td>
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</tr>
<tr>
<td>Nighttime SBP</td>
<td>116.5±15.0</td>
<td>111.8±11.9</td>
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<tr>
<td>Nighttime DBP</td>
<td>68.3±12.6</td>
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<td>Nighttime HR</td>
<td>70.2±13.3</td>
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<tr>
<td>Nighttime MAP</td>
<td>84.3±12.6</td>
<td>79.5±9.2</td>
<td>0.000</td>
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<tr>
<td>Nocturnal drop in SBP</td>
<td>10.7</td>
<td>12.2</td>
<td>0.341</td>
</tr>
<tr>
<td>Nocturnal drop in DBP</td>
<td>14.5</td>
<td>16.5</td>
<td>0.390</td>
</tr>
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</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure.
changes in BMC during treatment with pioglitazone. Nevertheless, with the currently available data on adverse effects of TZDs, the routine use of pioglitazone in CAH patients seems not to be indicated in a clinical setting.

Our study has limitations. Inherent to the short 16-week treatment period, we were not able to evaluate long-term effects of pioglitazone in our population. Furthermore, insulin sensitivity was used as a surrogate outcome, but no data on the prevalence of diabetes mellitus or cardiovascular disease are available. Furthermore, our study was probably underpowered to detect changes in fat distribution, fat mass, and liver fat.

In summary, this study shows that adult CAH patients treated with glucocorticoids are insulin resistant. Treatment with pioglitazone significantly improves insulin sensitivity and decreases blood pressure in CAH patients compared with the use of placebo. Despite these findings, there is currently not enough evidence to warrant the routine use of pioglitazone in this group of patients.

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

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