Pediatric Diabetes 2009
doi: 10.1111/j.1399-5448.2009.00512.x

Pediatric Diabetes

Original Article

Metformin therapy to reduce weight gain and visceral adiposity in children and adolescents with neurogenic or myogenic motor deficit

Casteels K, Fieuws S, van Helvoirt M, Verpoorten C, Goemans N, Coudyzer W, Loeckx D, de Zegher F. Metformin therapy to reduce weight gain and visceral adiposity in children and adolescents with neurogenic or myogenic motor deficit.
Pediatric Diabetes 2009.

The aim of this randomized, placebo-controlled study was to explore the effect of metformin in children with a neurogenic or myogenic motor deficit, who are therefore prone to develop overweight, adiposity, and insulin resistance.
Study participants (n = 42) had a mean age of 15.5 yr, a short stature (height −2.4 SD), a relatively high BMI (+1.7 SD), and a high body fat fraction (41.9% or +2.8 SD). Abdominal CT confirmed the high fat mass and disclosed a high fraction of visceral fat. As expected, insulin resistance was increased.
As compared to placebo, metformin intake for 6 months exerted an insulin sensitizing effect and lowered weight (mean difference of 2 kg within 6 months, $p = 0.007$) and BMI ($p = 0.016$). Weight loss appeared to be primarily due to loss of visceral fat (~20% vs. placebo; $p < 0.0001$). Results were similar across diagnostic subgroups.
In conclusion, metformin treatment for 6 months was associated with a rise in insulin sensitivity and with a reduction of visceral adiposity in children and adolescents with a primary muscle disorder or with a neural tube defect. These findings suggest that insulin resistance underpins, at least partly, the overweight and visceral adiposity of these patients, who are not necessarily obese.

Kristina Casteels[a], Steffen Fieuws[b], Maria van Helvoirt[a], Carla Verpoorten[a], Nathalie Goemans[a], Walter Coudyzer[c], Dirk Loeckx[d] and Francis de Zegher[a]

[a]Department of Pediatrics, UZ Leuven, Leuven, Belgium; [b]I-BioStat, Katholieke Universiteit Leuven and Universiteit Hasselt; [c]Department of Radiology, UZ Leuven, Leuven, Belgium; and [d]Medical Image Computing, ESAT/PSI, Faculty of Engineering, Katholieke Universiteit Leuven, Leuven, Belgium

Key words: body composition – insulin resistance – metformin – neural tube defect – neuromuscular disease

Corresponding author:
Kristina Casteels
Department of Pediatrics, UZ Leuven,
Herestraat 49, 3000 Leuven, Belgium.
Tel: 00 321 634 3840;
fax: 00 321 634 3842;
e-mail: Kristina.casteels@uzleuven.be

Submitted 13 October 2008. Accepted for publication 9 February 2009

Obesity with insulin resistance in the pediatric population provides an increasing challenge. Children with neurological or neuromuscular diseases are even more prone to obesity: their locomotor impairment leads to an increasingly sedentary lifestyle, a decrease in physical fitness and an increase in body fat (1–3). Obesity, in turn, can be associated with a decrease in physical fitness and a further increase in body fat.

In the literature various articles have been published on the prevalence of obesity in children with neurological or neuromuscular diseases [e.g. spina bifida, Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), quadriplegia. . .], but few studies have studied the prevalence of metabolic complications in these patients (4–7). Nelson et al. identified metabolic syndrome in 32.4 and 55% of adolescents with spina bifida and spinal cord injury,

respectively, and in another study 55% of 11 adults with neuromuscular diseases met the criteria for metabolic syndrome (7, 8).

In this study, we have evaluated the effect of an insulin-sensitizer, metformin, in a group of overweight/obese patients with neurological or neuromuscular diseases. Metformin is a well-established insulin sensitizer and the first line drug in the treatment of obese type 2 diabetes (9). Metformin is also beneficial in pediatric patients with type 1 diabetes and insulin resistance, in girls with or at risk of developing polycystic ovarian syndrome, in patients with type 2 diabetes or non-alcoholic fatty liver disease, and in patients with psychotropic drug-induced weight gain (10–20). Recently a randomized controlled trial showed improvement in body composition and fasting insulin in obese insulin-resistant adolescents (21).

The primary mechanism of action of metformin seems to be suppression of hepatic glucose production. Whether metformin improves peripheral insulin sensitivity has not been consistently demonstrated in previous clinical studies (22). Metformin action requires the enzyme AMP-activated protein kinase (AMPK). In general, activation of AMPK triggers catabolic pathways that produce ATP (e.g. lipid oxidation and glucose uptake), while turning off anabolic pathways that consume ATP (23). In mice, metformin requires LKB1 tumor suppressor in the liver to lower glucose levels and a recent article demonstrates that organic cation transporter1 (OCT1) is important for metformin's therapeutic action and that genetic variation in OCT1 may have an impact on the individual response to metformin (24,25). Some but not all studies indicate that metformin may have anti-inflammatory and lipolytic effects mediated through adipocytokines (26, 27).

Methods

Subjects

Patients with neurogenic or myogenic motor deficit were recruited during a 3 month period: patients who were clinically obese or who had excessively gained weight over the last year were asked whether they were interested to participate in the study. They were included if they met the following inclusion criteria: older than 8 yr of age, fat mass >30% (absorptiometry) or insulin resistance [screened by fasting glucose (mg/dl) over insulin (mU/l) <7] (28–30). Exclusion criteria were known type 1 or type 2 diabetes mellitus and hepatic or renal failure (31). All parents and patients received oral and written information about the study before providing written consent. The study was approved by the Ethical Review Board of the University Hospitals Leuven. The study was registered as NCT00720161.

Study design

Randomization (1:1 ratio for Group A vs. B) was stratified by diagnostic subgroup. Placebo and metformin capsules had the same appearance, and were given in the evening at a dose of 425 mg/d (age <10 yr) or 850 mg/d (age ≥10 yr). Patients and investigators, except for the study statistician (SF), remained blinded to intervention. Standard advice on a healthy diet and—if possible—exercise was given to all patients. Diaries were maintained to judge treatment compliance.

The timeline for investigations is illustrated in Fig. 1. At a 6-monthly interval, the participants attended the day care hospital after 8 h of fasting for clinical assessment including anthropometry, a fasting blood analysis, an oral glucose tolerance test (OGTT), and body composition by absorptiometry and CT abdomen as detailed later.

Blood analysis, hormone assays, and OGTT

Fasting blood sample included a total blood count, a lipidogram, ureum, and creatinin and liver function tests. An OGTT was performed with 1.75 g/kg glucose (maximum 75 g). Blood samples were obtained at 0, 30, 60, and 120 min for measurement of serum glucose and insulin. Insulin sensitivity was evaluated based on the homeostasis model assessment (HOMA-CIGMA Calculator program version v2.00, Oxford, UK).

Absorptiometry

Body composition was assessed by dual-energy x-ray absorptiometry using a QDR-Discovery A, coupled to corresponding software (v12.3:3; Hologic, Waltham, MA, USA). Patients were positioned on the scanner table according to standard procedures

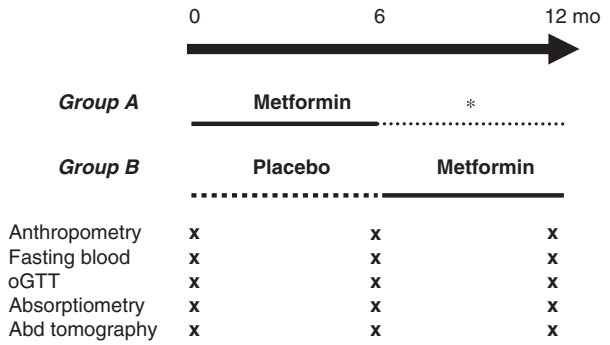

Fig. 1. Study analysis. The main comparisons were between 6-months changes on placebo vs. metformin. To increase the power of these comparisons, the 6-months changes on metformin in group A (0–6 months) were compiled with the 6-months changes on metformin in group B (6–12 months). *6–12 months changes in group A (on metformin) is not involved in the test from the multivariate regression model to assess the effect of metformin.

for anterior-posterior scanning. All total-body scans and regional analyses were performed by two certified technicians (also blinded to treatment).

Abdominal tomography

To assess abdominal fat partitioning (subcutaneous vs. visceral), three axial images were obtained by tomography (thickness of 3 mm) with one rotation (12×0.75 mm) only at L3–L4 disk level, and this to minimize radiation exposure (0.5 mSv). Images were recorded on the same Sensation 16 scanner (Siemens, Erlangen, Germany). Each of the three images was analyzed separately. In each image, body contour was delineated. A range of -424 to 3072 HU (Hounsfield units) was used for analysis of the total area of the axial section and the range for fat measurements was -190 to -30 HU (32–35). The areas of intra- and extra-abdominal fat (visceral vs. subcutaneous) were delineated by a single investigator (WC, blinded to treatment), respectively inside and outside the muscle wall around the abdominal cavity. Results derived from the three images (per assessment) were averaged; fat areas were expressed in square centimeters; visceral fat was also expressed as a fraction of visceral-plus-subcutaneous fat. The present method was used to avoid interference of intramuscular lipid deposition, which may be exaggerated in patients with neuromuscular disease.

Statistical analysis

Except for the study statistician (SF) all investigators remained blinded to treatment assignment at least until completion of the present report. The aim of this study was to compare the effect of metformin therapy during 6 months with the effect of 6 months of placebo. To increase the power of the analysis, the information on the changes after 6 months of metformin in group B were also used in the comparison of both groups (see Fig. 1). Multivariate regression models with an unstructured covariance matrix were used to model the repeated measures (three time points) for each of the considered outcomes separately. Using the SAS-procedure PROC MIXED (SAS, version 9.1), all available information was used in the analysis, even if a subject had missing measurements at one or two points in time. As such, the analysis can be considered as a repeated measures analysis for incomplete data. The crucial test pertained the comparison of the average change after metformin (i.e. 0–6 months change in group A and 6–12 months change in group B) with the average change after placebo (0–6 months change in group B). Note that the validity of this comparison was based on the assumption that the observed change between baseline and 6 months in group B is an unbiased estimate of the (unobserved) change in a 6 months placebo period preceding baseline in group A. If needed, transformations (square-root or natural logarithm) were used to obtain a symmetric distribution of the residuals from the regression model. An intent-to-treat as well as an as-treated analysis were performed. In the latter analysis, the results from subjects admitted not to have taken their pills on a regular basis were ignored.

Results

Forty-four patients were referred to the study; two did not meet the inclusion criteria: both had a fat mass $<30\%$ and were not insulin resistant. Forty-two participated in the study: 22 patients with spina bifida (SB), 13 patients with DMD of which 12 received Deflazacort (0.6 mg/kg/day), and 7 patients with other neuromuscular diseases. Nineteen were randomized to receive metformin (group A) and 23 received 6 months of placebo before metformin (group B). After 6 months, one patient in group A was lost to follow-up, three discontinued due to social and familial circumstances and one girl due to side effects (nausea and diarrhea). In group B, two patients discontinued the study: one after 6 months due to social reasons and another after 12 months due to other medical problems. The flow of patients through the study is summarized in Fig. 2.

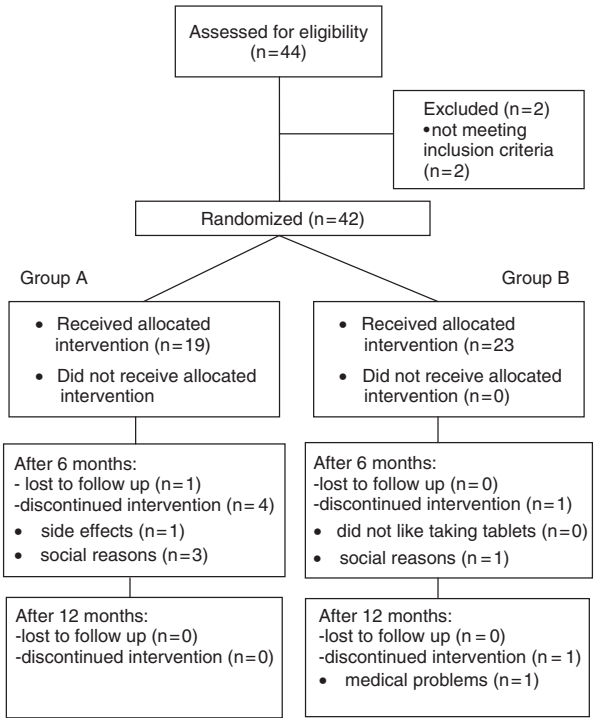

Fig. 2. CONSORT (Consolidated Standard for Reporting Clinical Trials) flow diagram.

Table 1. Baseline characteristics for all patients together

	Total Group (n = 42)	DMD (n = 13)	Spina bifida (n = 22)	Others (n = 7)
Age (yr)	15.5 ± 6.2	12.4 ± 2.8	17.2 ± 6.9	16.1 ± 7
Weight (kg)	54 ± 15	44 ± 10	59 ± 14	58 ± 6
Weight z-score	0.4 ± 1.2	0 ± 1.3	0.5 ± 1.3	1.0 ± 0.4
Height (cm)	142.5 ± 12.4	137 ± 10.1	143.3 ± 12.1	150.3 ± 13.8
Height z-score	−2.4 ± 2.1	−2.5 ± 1.9	−2.8 ± 2.3	−0.9 ± 0.9
BMI (kg/m^2)	26.5 ± 6.0	23.4 ± 4.1	28.8 ± 6.5	25.1 ± 5.0
BMI z-score	1.7 ± 0.7	1.4 ± 0.7	1.9 ± 0.7	1.5 ± 0.5
Waist (cm)†	85 ± 15	80 ± 12	88 ± 16	84 ± 14
% fat (DXA)	41.9 ± 7.0	41.1 ± 6.3	40 ± 5.6	49.6 ± 7.8
% fat z-score	2.8 ± 0.7	2.7 ± 0.5	2.6 ± 0.7	3.6 ± 0.9
Subcut fat (cm^2)*,#	228 ± 107.5	173 ± 86.9	248 ± 95.3	293 ± 136.9
Visceral fat (cm^2)*,#	76 ± 35	69 ± 22	77 ± 46	89 ± 16
Ratio visc/(visc+subc)*	0.26 ± 0.09	0.3 ± 0.09	0.24 ± 0.09	0.24 ± 0.04
Syst BP (mmHg)	123 ± 17	115 ± 8	125 ± 19	128 ± 18
Diast BP (mmHg)	74 ± 11	69 ± 5	75 ± 11	80 ± 13
Cholesterol (mg/dl)†	161 ± 33	164 ± 33	158 ± 32	166 ± 40
Glucose 0′ (mg/dl)	81 ± 8	77 ± 8	83 ± 7	83 ± 8
Insuline 0'(mU/l)‡	12 ± 6	10 ± 4	13 ± 6	17 ± 9
HOMA-R*	1.5 ± 0.8	1.2 ± 0.4	1.5 ± 0.8	2.1 ± 1.1
Glucose 120'(mg/dl)*	116 ± 19	104 ± 15	122 ± 19	121 ± 22
IFG	1	0	1	0
IGT	5/36	0/11	3/19	2/6

Information is based on 42 subjects, unless otherwise indicated; †:n = 41, ‡:n = 37, *:n = 36. Ratio visc/(visc + subc), ratio of visceral fat over visceral + subcutaneous fat (measured by CT); IFG, impaired fasting glucose; IGT, impaired glucose tolerance. #Mean values for visceral fat in 13 yr-old normal-weight and obese adolescents are 25 and 88 cm^2, respectively and for subcutaneous fat 127 and 542 cm^2 (41).

Baseline characteristics

We refer to Tables 1 to 2 for an overview of the baseline characteristics of the study patients. The mean age of the participants was 15.5 ± 6.2 yr. There were 19 boys and 23 girls.

Noteworthy are the low height (−2.4 SD), the relatively high BMI (+1.7 SD), and the high fat fraction: DXA scan revealed a mean percentage of body fat of 41.9% with a z-score of 2.8 SD. This z-score is based on the recently published gender-specific body fat reference curves by McCarthy et al. The 50th centile for 15 yr old girls is 24.1% and for boys 15.8% (36). CT abdomen confirmed the high fat mass with a high proportion of visceral fat [mean ratio visceral fat (cm^2)/visceral + subcutaneous fat (cm^2) = 0.27 ± 0.09]. As expected, HOMA-R was increased (1.5 ± 0.8) (28) and 5 of 36 patients had impaired glucose tolerance. When focussing on the

Table 2. Baseline characteristics per therapeutic group

	Placebo	Metformin
Age (yr)	15 ± 6	16 ± 6
Weight (kg)	55 ± 14	54 ± 16
Weight z-score	0.3 ± 1.6	0.5 ± 0.7
Height (cm)	141 ± 14	144 ± 10
Height z-score	−2.5 ± 2.3	−2.3 ± 2.0
BMI (kg/m^2)	27 ± 6	26 ± 6
BMI z-score	1.7 ± 0.7	1.7 ± 0.7
Waist (cm)†	86 ± 17	83 ± 11
% fat (DXA)	42 ± 7	42 ± 7
% fat z-score	2.8 ± 0.8	2.8 ± 0.7
Subcut fat (cm^2)*,#	244 ± 133	226 ± 95
Visceral fat (cm^2)*,#	83 ± 53	80 ± 48
Ratio visc/(visc+subc)*	0.38 ± 0.17	0.37 ± 0.18
Syst BP (mmHg)	121 ± 17	125 ± 16
Diast BP (mmHg)	73 ± 9	74 ± 13
Cholesterol (mg/dl)†	161 ± 31	169 ± 35
Glucose 0′ (mg/dl)	80 ± 8	82 ± 8
Insuline 0'(mU/l)‡	12 ± 5	15 ± 7
HOMA-R*	1.5 ± 0.6	1.8 ± 0.9
Glucose 120'(mg/dl)*	116 ± 22	116 ± 18
IFG	1	0
IGT	3	2

Information is based on 42 subjects, unless otherwise indicated; †:n = 41, ‡:n = 37, *:n = 36. Ratio visc/(visc + subc), ratio of visceral fat over visceral + subcutaneous fat (measured by CT); IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
#Mean values for visceral fat in 13 yr-old normal-weight and obese adolescents are 25 and 88 cm^2, respectively and for subcutaneous fat 127 and 542 cm^2 (41).

Table 3. Metformin treatment effect

Outcomes	Δ0–6 months Placebo	Δ0–6 months Metformin	p-value
Weight (kg)	1.92 (0.98; 2.87)	0.32 (−0.54; 1.19)	0.0072
BMI (kg/m^2)	0.68 (0.13; 1.24)	−0.28 (−0.72; 0.17)	0.016
BMI z-score	0.05 (−0.04; 0.15)	−0.15 (−0.23; −0.06)	0.0015
CT patient* (cm^2)	1.06 (1.02; 1.11)	1.0 (0.97; 1.04)	0.049
CT fat*(cm^2)	1.11 (1.04; 1.19)	1.0 (0.95; 1.06)	0.023
CT subcutaneous fat*(cm^2)	1.12 (1.02; 1.22)	1.04 (0.95; 1.14)	0.31
CT visceral fat*(cm^2)	1.12 (1.03; 1.21)	0.92 (0.85; 0.99)	0.0008
CT % fat	2.2 (−0.2; 4.6)	−0.1 (−2.1; 2)	0.18
CT % subcutaneous fat	1.2 (−1.2; 3.6)	1.7 (−1; 4.4)	0.82
CT % visceral fat	0.8 (−0.3; 2)	− 1.4 (−2.4; −0.4)	0.005
%fat (DXA)	0.64 (−0.06; 1.35)	0.13 (−0.45; 0.72)	0.26
%fat z-score	0.08 (−0.01; 0.16)	−0.01 (−0.08; 0.05)	0.11
Glucose 0 (mg/dl)	3.3 (0.7; 5.8)	−1.3 (−3.3; 0.7)	0.015
Insulin 0' (mg/dl)	1.9 (−0.1; 4.1)	−1.1 (−2.7; 0.6)	0.058
Insulin 30' (mg/dl)	19.8 (−24.7; 72.2)	−21.2 (−49.7; 11.8)	0.16
Insulin 60'*	1.50 (1.14; 1.96)	0.88 (0.71; 1.09)	0.006
Insulin 120'*	1.44 (1.08; 1.93)	0.96 (0.78; 1.18)	0.036
HOMA S*	0.86 (0.73; 1)	1.11 (0.97; 1.28)	0.037
HOMA R	0.25 (−0.01; 0.53)	−0.15 (−0.35; 0.06)	0.044
HOMA B	3.6 (−17.3; 24.4)	−4.6 (−21.9; 12.8)	0.60
Insulin Index	0.030 (0.002; 0.061)	−0.01 (−0.031; 0.013)	0.04
Cholesterol*	0.96 (0.90; 1.01)	0.99 (0.94; 1.04)	0.40
Triglycerides*	0.99 (0.78; 1.24)	1.20 (0.99; 1.47)	0.29

Changes and 95% confidence interval (CI) after 6 months placebo (obtained from placebo–metformin group) and after 6 months metformin (obtained from both groups). The p-value pertains to the comparison of the changes (hence, to the effect of metformin). Note that when the analysis is based on log-transformed measurements (outcomes are indicated with *), the changes are expressed as a ratio. When a square root transformation is applied, the change is given on the original scale, for a subject with a median starting level. Positive numbers (or numbers >1 for log-transformed outcomes) reflect an increase.

older study groups (spina bifida and other), the rate of insulin resistance was even higher: 20% (5/25) of the patients had impaired glucose tolerance.

Metformin treatment effect on glucose metabolism and lipids

As compared to placebo, metformin therapy exerted a beneficial effect on insulin sensitivity (HOMAR, $p = 0.044$) (Fig. 3 and Table 3). Beneficial changes were observed for fasting glucose ($p = 0.015$); fasting insulin ($p = 0.058$); and insulin at 30, 60, and 120 min ($p = 0.16$, $p = 0.006$, and $p = 0.036$, respectively). There was no difference between the effect of metformin and placebo on cholesterol and triglycerides levels.

Metformin treatment effect on anthropometry and body composition

Metformin had a significant beneficial treatment effect over placebo on weight ($p = 0.0072$) and BMI ($p = 0.016$) (Fig. 4 and Table 3). Metformin did not result in a significant reduction in total body fat (measured by DEXA or CT scan) but interestingly, there was a highly significant beneficial effect on visceral fat ($p = 0.0008$), suggesting that the weight loss was primarily due to a reduction in visceral fat.

The results of this analysis were comparable to the results seen after analysis of changes between baseline and 6 months in both groups (results not shown). This finding validates the combination of both metformin periods to increase the power of the analysis.

In this article the p-values are derived from intent-to-treat analysis; results are comparable with the as-treated analysis.

Side effects, safety profile, and adherence to therapy

Both metformin (850 mg) and placebo were well tolerated. Only one patient discontinued the study because of side effects (diarrhea). Three other patients experienced abdominal discomfort which was resolved by temporarily lowering the dose. Peripheral blood count and indices of hepatic and renal function remained unchanged throughout therapy. Adherence to therapy based on patient diaries was similar for metformin and placebo. After 12 months four patients admitted not to have taken their pills on a regular basis:

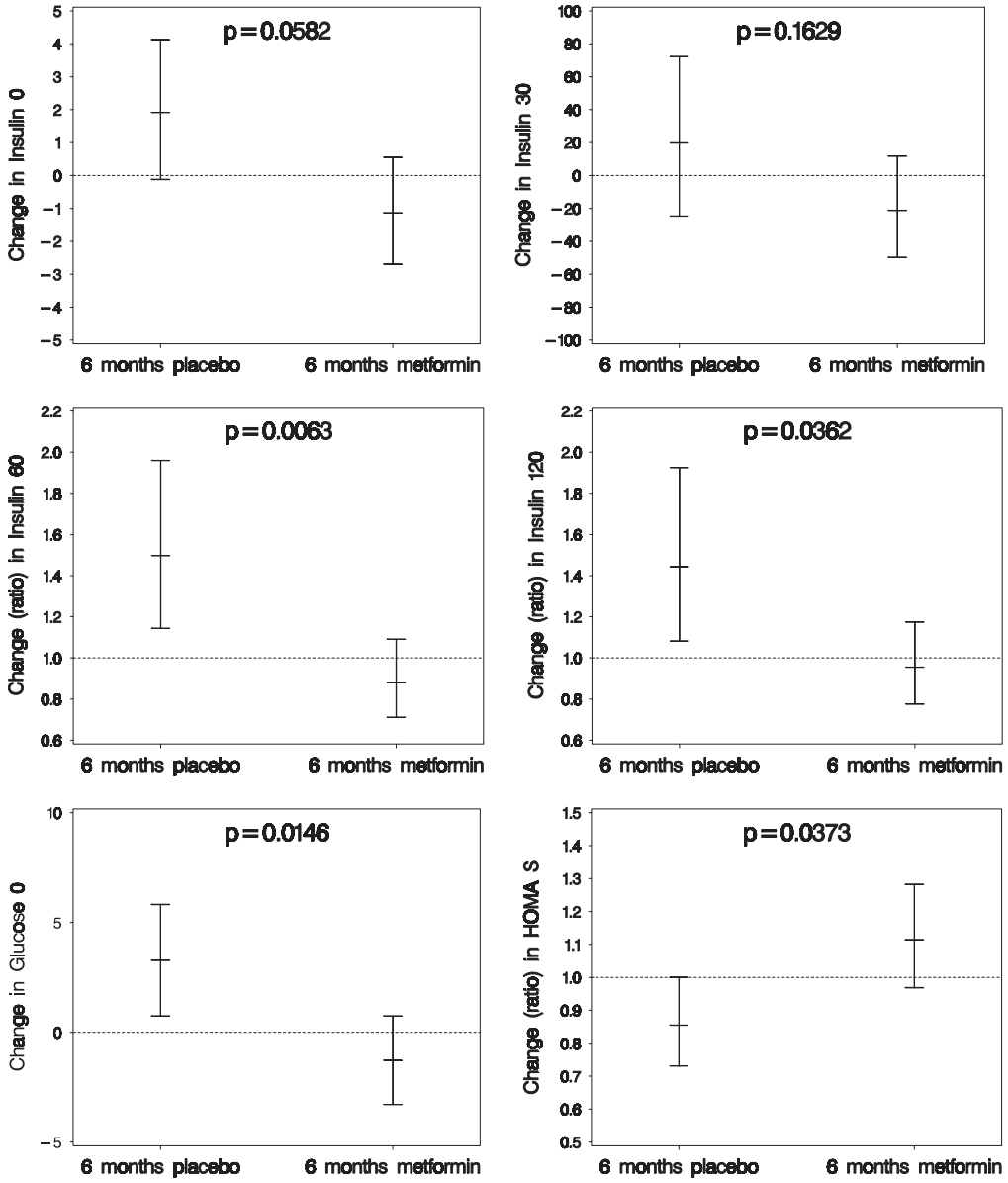

Fig. 3. Changes in insulin, fasting glucose, and HOMA S after 6 months metformin and 6 months placebo. Vertical lines denote the 95% CI of the change. Note that when the analysis is based on log-transformed measurements, the changes are expressed as a ratio. The p-value pertains to the comparison of the changes.

therefore an intent-to-treat as well as an as-treated analyses were performed.

Discussion

In children with a neurogenic or myogenic motor deficit, both overweight and adiposity tend to increase over time, and may thus become an additional burden for these patients and their environment.

In this study, the effect of metformin was evaluated in a group of patients with neurological or neuromuscular disease and with increased fat percentage. The mean BMI SD was 1.7 ± 0.7 and the percentage of fat was very high (mean body fat: 41.9%).

A recent article by Taksali et al. clearly describes that adolescents with a high proportion of visceral fat (and thus a high ratio of visceral fat/(visceral + subcutaneous fat)) are at high risk for metabolic complications (36, 37). In their study, abdominal fat was measured by MRI. The cohort was stratified into tertiles based on the proportion of abdominal fat, and it was demonstrated that the children in tertile 3 (highest ratio: ratio between 0.122 and 0.224) had the highest risk for metabolic syndrome. The proportion of visceral fat in our study population was even higher and the mean ratio was 0.27. To mention however is the fact

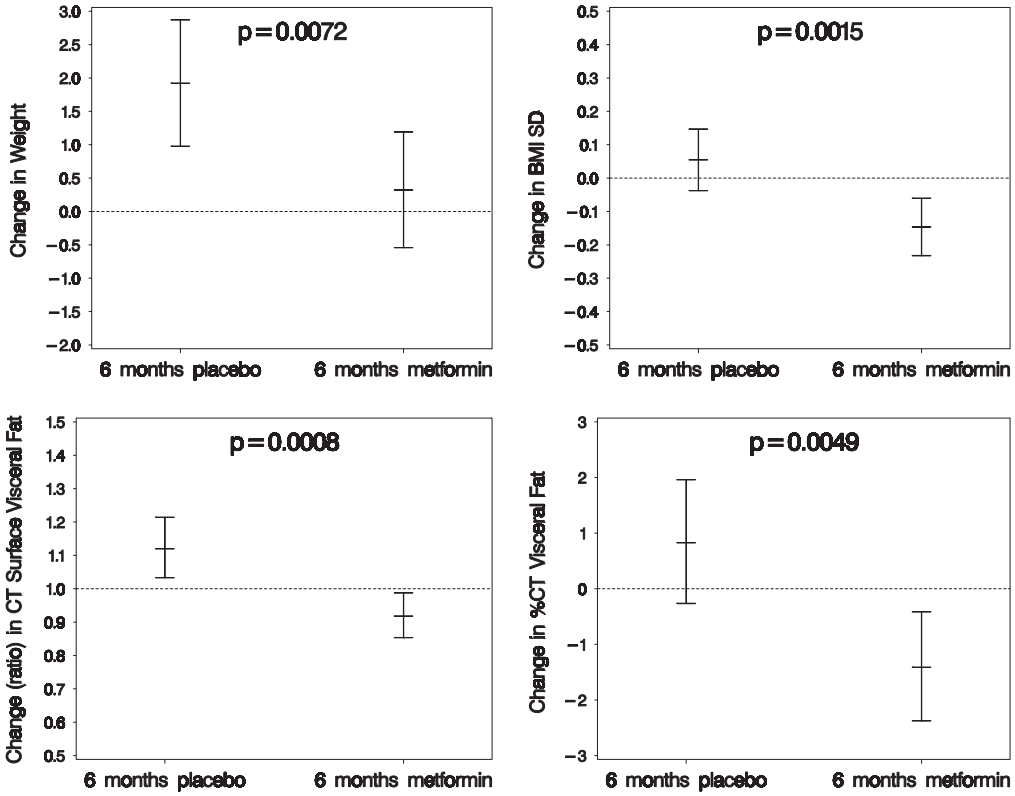

Fig. 4. Changes in weight, BMI SD, and visceral fat as measured by CT after 6 months metformin and 6 months placebo. Vertical lines denote the 95% CI of the change. The p-value pertains to the comparison of the changes.

that abdominal tomography (and not MRI) was used in our study.

Metformin treatment (850 mg/d for 6 months) is clearly associated with a rise in insulin sensitivity and with a reduction in weight, BMI, and in particular of visceral adiposity (~20% vs. placebo; $p < 0.0001$).

These observations suggest that insulin resistance contributes to drive the vicious circle toward escalating overweight and visceral adiposity in young patients with a motor deficit.

These results confirm previously described effects of metformin in non-obese, insulin-resistant girls with a combined history of low birthweight and either precocious pubarche or early-normal puberty: in such girls, prolonged metformin treatment (for up to 4 yr) also attenuated weight gain by reducing the gain of fat, including visceral fat (10–16). Metformin is also beneficial in young patients with type 2 diabetes, pediatric patients with type 1 diabetes and insulin resistance, young patients with non-alcoholic fatty liver disease, in patients with exogenous obesity and insulin resistance, and in patients with psychotropic drug-induced weight gain (17–21).

Twelve of thirteen patients with DMD received Deflazacort and so it is impossible to compare the differential effect of metformin in patients with or without Defalzacort. The observations however in Deflazacort-treated boys with DMD align well with the recent insight that glucocorticoids may induce overweight and central adiposity via a down-regulation of the adenosine-monophosphate-dependent kinase (AMPK) pathway. AMPK is activated by decreases in the energy state of a cell and once activated AMPK switches of anabolic pathways such as fatty acid-, triglyceride-, cholesterol-, and protein synthesis and switches on catabolic pathways such as glycolysis and fatty acid oxidation. Metformin is known to upregulate this pathway, and may thereby reverse the described glucocorticoid-induced down-regulation of AMPK activity (38, 39).

In conclusion, metformin treatment (850 mg for 6 months) exerts insulin-sensitizing effects and reduces the gains of weight and of visceral adiposity in children and adolescents with a muscle disorder or a neural tube defect. Future studies will disclose whether such metformin effects wane, persist, or amplify over time.

Acknowledgements

The present work was supported by the Fund for Scientific Research (G.0326.06); KC and FdZ are Clinical Investigators, and DL is a Postdoctoral Fellow, each of the Fund for Scientific Research (Flanders, Belgium).

References

1. Liusuwan RA, Widman LM, Abresch RT, Styne DM, McDonald CM. Body composition and resting energy expenditure in patients aged 11 to 21 yr with spinal cord dysfunction compared to controls: comparisons and relationships among the groups. J Spinal Cord Med 2007: 30: S105–S111.
2. van den Berg-Emons HJ, Bussmann JB, Meyerink HJ, Roebroeck ME, Stam HJ. Body fat, fitness and level of everyday physical activity in adolescents and young adults with meningomyelocele. J Rehabil Med 2003: 35: 271–275.
3. Widman LM, Abresch RT, Styne DM, McDonald CM. Aerobic fitness and upper extremity strength in patients aged 11 to 21 yr with spinal cord dysfunction as compared to ideal weight and overweight controls. J Spinal Cord Med 2007: 30(Suppl 1):S88–S96.
4. Mok E, Béghin L, Gachon P et al. Estimating body composition in children with Duchenne muscular dystrophy: comparison of bioelectrical impedance analysis and skinfold-thickness measurement. J Spinal Cord Med 2006: 30(Suppl 1):S88–S96.
5. Leroy-Willig A, Willig TN, Henry-Feugeas MC et al. Body composition determined with MR in patients with Duchenne muscular dystrophy, spinal muscular atrophy, and normal subjects. J Spinal Cord Med 2007: 30(Suppl 1):S88–S96.
6. McDonald CM, Carter GT, Abresch RT et al. Body composition and water compartment measurements in boys with Duchenne muscular dystrophy. Am J Phys Med Rehabil 2005: 84: 483–491.
7. Aitkens S, Kilmer DD, Wright NC, McCrory MA. Metabolic syndrome in neuromuscular disease. Arch Phys Med Rehabil 2005: 86: 1030–1036.
8. Nelson MD, Widman LM, Abresch RT et al. Metabolic syndrome in adolescents with spinal cord dysfunction. Arch Phys Med Rehabil 2007: 86: 1030–1036.
9. American Diabetes Association. Standards of medical care in diabetes.Diabetes Care 2008: 31: S12–S54.
10. Ibáñez L, López-Bermejo A, Díaz M, Marcos MV, de Zegher F. Metformin treatment for four years to reduce total and visceral fat in low birth weight girls with precocious pubarche. J Clin Endocrinol Metab 2008: 93: 1841–1845.
11. Ibáñez L, Ong K, Valls C, Marcos MV, Dunger DB, de Zegher F. Metformin treatment to prevent early puberty in girls with precocious pubarche. J Clin Endocrinol Metab 2006: 91: 2888–2891.
12. Ibáñez L, Valls C, Ong K, Dunger DB, de Zegher F. Metformin therapy during puberty delays menarche, prolongs pubertal growth, and augments adult height: a randomized study in low-birth-weight girls with early-normal onset of puberty. J Clin Endocrinol Metab 2006: 91: 2068–2073.
13. Ibáñez L, Valls C, Marcos MV, Ong K, Dunger DB, de Zegher F. Insulin sensitization for girls with precocious pubarche and with risk for polycystic ovary syndrome: effects of prepubertal initiation and postpubertal discontinuation of metformin treatment. J Clin Endocrinol Metab 2004: 89: 4331–4337.
14. Ibáñez L, Ferrer A, Ong K, Amin R, Dunger D, de Zegher F. Insulin sensitization early after menarche prevents progression from precocious pubarche to polycystic ovary syndrome. J Clin Endocrinol Metab 2004: 89: 4331–4337.
15. Ibáñez L, Potau N, Ferrer A, Rodriguez-Hierro F, Marcos MV, de Zegher F. Anovulation in eumenorrheic, nonobese adolescent girls born small for gestational age: insulin sensitization induces ovulation, increases lean body mass, and reduces abdominal fat excess, dyslipidemia, and subclinical hyperandrogenism. J Clin Endocrinol Metab 2002: 7: 5702–5705.
16. Ibáñez L, Lopez-Bermejo A, Suárez L, Marcos MV, Díaz M, de Zegher F. Metformin treatment for four years to reduce total and visceral fat in low birth weight girls with precocious pubarche. J Clin Endocrinol Metab 2008: 93: 1841–1845.
17. Gómez R, Mokhashi MH, Rao J, et al. Metformin adjunctive therapy with insulin improves glycemic control in patients with type 1 diabetes mellitus: a pilot study. J Pediatr Endocrinol Metab 2002: 15: 1147–1151.
18. Jones KL, Arslanian S, Peterokova VA, Park JS, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. Diabetes Care 2002: 25: 89–94.
19. Schwimmer JB, Middleton MS, Deutsch R, Lavine JE. A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2005: 21: 871–879.
20. Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA. A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. Am J Psychiatry 2006: 163: 2072–2079.
21. Srinivasan S, Ambler GR, Baur LA et al. Randomized, controlled trial of metformin for obesity and insulin resistance in children and adolescents: improvement in body composition and fasting insulin. J Clin Endocrinol Metab 2006: 91: 2074–2080.
22. Bailey CJ, Turner RC. Metformin. N Engl J Med 1996: 334: 574–579.
23. Shaw RJ, Lamia KA, Vasquez D et al. The kinase LKB1 mediates glucose homeostasis in liver and therapeutic effects of metformin. Science 2005: 310: 1642–1646.
24. Reitman ML, Schadt EE. Pharmacogenetics of metformin response: a step in the path toward personalized medicine. J Clin Invest 2007: 117: 1226–1229.
25. Shu Y, Sheardown SA, Brown C et al. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. J Clin Invest 2007: 117: 1422–1431.
26. Ibáñez L, de Zegher F. Flutamide-metformin plus ethinylestradiol-drospirenone for lipolysis and antiatherogenesis in young women with ovarian hyperandrogenism: the key role of metformin at the start and after more than one year of therapy. J Clin Endocrinol Metab 2005: 90: 39–43.
27. De Jager J, Kooy A, Lehert P et al. Effects of short-term treatment with metformin on markers of endothelial function and inflammatory activity in type 2 diabetes mellitus: a randomized, placebo-controlled trial. J Intern Med 2005: 257: 100–109.

28. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab 2008: 294: E15–E26.
29. Silfen ME, Manibo AM, McMahon DJ, Levine LS, Murphy AR, Oberfield SE. Comparison of simple measures of insulin sensitivity in young girls with premature adrenarche: the fasting glucose to insulin ratio may be a simple and useful measure. J Clin Endocrinol Metab 2001: 86: 2863–2868.
30. Vicini P, Caumo A, Cobelli C. The hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity. Am J Physiol. 1997: 273: E1024–E1032.
31. Tahrani AA, Varughese GI, Scarpello JH, Hanna FW. Metformin, heart failure, and lactic acidosis: is metformin absolutely contraindicated? BMJ 2007: 335: 508–512.
32. Ferland M, Després JP, Tremblay A, et al. Assessment of adipose tissue distribution by computed axial tomography in obese women: association with body density and anthropometric measurements. Br J Nutr 1989: 61: 139–148.
33. Seidell JC, Oosterlee A, Thijssen MA et al. Assessment of intra-abdominal and subcutaneous abdominal fat: relation between anthropometry and computed tomography. Am J Clin Nutr 1987: 45: 7–13.
34. Bray GA, Jablonski KA, Fujimoto WY et al. Relation of central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. Am J Clin Nutr 2008: 87: 1212–1218.
35. von Eyben FE, Mouritsen E, Holm J et al. Intra-abdominal obesity and metabolic risk factors: a study of young adults. Int J Obes Relat Metab Disord 2003: 27: 941–949.
36. McCarthy HD, Cole TJ, Fry T, Jebb SA, Prentice AM. Body fat reference curves for children. Int J Obesity 2006: 30: 598–602.
37. Taksali SE, Caprio S, Dziura J et al. High visceral and low abdominal subcutaneous fat stores in the obese adolescent: a determinant of an adverse metabolic phenotype. Diabetes 2008: 57: 367–371.
38. Després JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med 2006: 38: 52–63.
39. Christ-Crain M, Kola B, Lolli F et al. AMP-activated protein kinase mediates glucocorticoid-induced metabolic changes: a novel mechanism in Cushing's syndrome. FASEB J 2008: 22: 1672–1683.
40. Hardie DG. AMPK: a key regulator of energy balance in the single cell and the whole organism. Int J Obes (Lond) 2008: 32(Suppl 4):S7–12.
41. Bacha F, Saad R, Gungor N, Arslanian S. Adiponectin in youth. Relationship to visceral adiposity, insulin sensitivity, and beta-cell function. Diabetes Care 2004: 27: 547–552.