

Pubertal Metformin Therapy to Reduce Total, Visceral, and Hepatic Adiposity

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Objective Puberty is part of a critical window in which adiposity and its correlates can be fine-tuned toward reproduction, which implies that puberty provides an opportunity to reprogram a misprogramming that occurred in early life. We tested this hypothesis in low-birthweight (LBW) girls with precocious pubarche (PP), who are at risk for hyperinsulinemic body adiposity during and beyond puberty.

Study design LBW girls with PP ($n = 38$; mean age 8 years) were randomized to remain untreated or to receive metformin across puberty (425 mg/d for 2 years, then 850 mg/d for 2 years); subsequently, all girls were monitored for 1 year without intervention. Here we report on the latter year.

Results The benefits of metformin were mostly maintained during the posttreatment year so that, after 5 years, metformin therapy was associated with more lean mass; with less total, visceral, and hepatic fat; with lower circulating levels of androgens and leptin; and with elevated levels of high-molecular-weight adiponectin and undercarboxylated osteocalcin.

Conclusion In LBW girls with PP, pubertal metformin therapy was followed by a favorable adipokine profile and by a reduction of total, visceral, and hepatic adiposity beyond puberty. (*J Pediatr* 2010;156:98-102).

The sequence of prenatal growth restraint and postnatal excess of visceral fat is believed to result from a mismatch between the prenatally programmed epigenome and the postnatally encountered environment and confers long-term metabolic and cardiovascular risk.¹ The epigenome seems to maintain some plasticity in childhood and also in puberty.²⁻⁵ Accordingly, puberty may still be part of a critical window in which endocrine-metabolic settings can be fine-tuned towards reproduction. This concept implies that puberty provides an opportunity to reprogram a misprogramming that may have occurred in early life. We tested this hypothesis in low-birthweight (LBW) girls, who exaggerated their catch-up of weight in early childhood,⁶ who had development of precocious pubarche (PP; pubic hair before age 8 years), and who are therefore at risk for development of an adipose body composition, with early onset of puberty, rapid progression to menarche, and, ultimately, with hyperinsulinemic androgen excess or polycystic ovary syndrome.⁷⁻¹⁴ We tested this hypothesis with metformin, whose actions seem to be largely exerted through activation of adenosine monophosphate-activated protein kinase, a conserved regulator of the cellular response to low energy in the liver. This activation is catalyzed by serine-threonine-kinase (formerly known as LKB1). The effects of metformin thus mimic—but are not necessarily as efficacious as—the effects of physical exercise or caloric restriction.¹⁵⁻¹⁸

Methods

The study population consisted of 38 LBW girls with PP, distributed in 2 well-matched subgroups of 19 girls each, whose baseline characteristics have been reported.¹⁷ In the total population, birthweight (mean $\pm$ SEM) was 2.4 ± 0.1 kg after 38.6 ± 0.4 weeks (17 of the 19 untreated girls, and 18 of the 19 treated girls were born at term), age at diagnosis of PP was 6.8 ± 0.2 years, age at study start 7.9 ± 0.1 years, bone age 9.0 ± 0.1 years, height 129.4 ± 1.2 cm, weight 31.0 ± 0.9 kg, BMI 18.4 ± 0.3 kg/m², dehydroepiandrosterone sulfate (DHEAS) at PP diagnosis 102 ± 6 μ g/dL, and post-adrenocorticotrophic hormone 17-hydroxy-progesterone 274 ± 16 ng/dL.

AI	Average intensity
DHEAS	Dehydroepiandrosterone sulfate
HMW	High-molecular-weight
IGF-1	Insulin-like growth factor 1
IHLIC	Intrahepatic lipid content
LBW	Low-birthweight
MRI	Magnetic resonance imaging
PP	Precocious pubarche
SHBG	Sex hormone binding globulin

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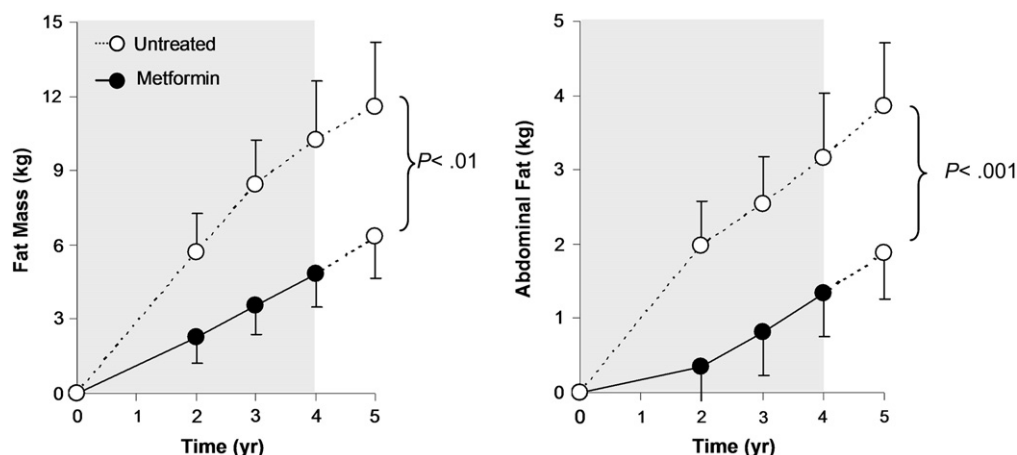


Figure 1. Cumulative gain in total and abdominal fat mass in prepubertal girls (age ~ 8 years) with a history of LBW and PP, who were randomized to remain untreated ($n = 19$; open circles) or to receive metformin ($n = 19$; closed circles) for 4 years, and who were then followed up for 1 year without intervention. Pubertal metformin treatment reduced fat gain not only across puberty, but also beyond puberty. Mean and 95% CI are shown. Difference in rate of change between subgroups significant by repeated-measures analysis of variance.

As described,¹⁷ the inclusion criteria were as follow: (1) PP because of exaggerated adrenarche, as judged by high serum DHEAS or androstenedione levels; (2) weight < 2.9 kg at term birth (38-41 weeks) or less than 1 SD for gestational age at preterm birth (33-37 weeks); (3) body mass index (BMI) < 22 kg/m², which corresponds to the +2 SD cutoff in girls aged ~ 8 years; and (4) prepuberty (Tanner B1). None of the girls had a family or personal history of diabetes mellitus or presented evidence for thyroid dysfunction, glucose intolerance, or late-onset congenital adrenal hyperplasia; none was receiving a medication known to affect gonadal function or carbohydrate metabolism. In the inclusion criteria, the cutoff for term birthweight was based on earlier evidence,⁷⁻⁹ and the cutoff for preterm birthweight was arbitrarily set at -1 SD, given the emerging evidence that premature birth may by itself have programming effects.

The study was registered as ISRCTN84749320 and was approved by the Institutional Review Board of Barcelona University, Hospital of Sant Joan de Déu. Informed consent was obtained from parents and assent from girls.

Girls were randomly assigned, as described,^{16,17} to remain untreated or to receive metformin for 4 years, once daily at dinner time (425 mg for 2 years, then 850 mg for 2 years, the body weight of the treated girls on average exceeded 40 kg after 2 years of study). At start of study, the hypothesis was that hyperinsulinemic insulin resistance was largely responsible for the endocrine-metabolic profile and for the clinical phenotype of LBW girls with PP.¹⁶ Lifestyles were similar in the randomized subgroups, as documented by profiles of dietary intake and physical activity over 4 years.¹⁸ Metformin tolerance and treatment compliance over 4 years were excellent.¹⁸ Subsequently, all girls were monitored for 1 year without intervention, the total study duration thus being 5 years.

Because most results after 6 months,¹⁶ after 1 and 2 years,¹⁷ and after 4 years¹⁸ have been reported when they became available, we will focus here on changes between 0 to 5 years, on changes between 4 to 5 years, and on outcomes after 5 years.

Clinical examination was performed every 6 months by the same investigator (L.I.); assessment of serum insulin, fasting blood glucose, sex hormone binding globulin (SHBG), testosterone, DHEAS, a lipid profile, and body composition were each performed every 6 months for 2 years, and yearly thereafter. Serum leptin, high-molecular-weight (HMW) adiponectin, and undercarboxylated osteocalcin were all measured at 0, 4, and 5 years. Undercarboxylated osteocalcin is the fraction of circulating osteocalcin that is believed to have adiponectin-raising and insulin-sensitizing effects. Height was measured with a Harpenden stadiometer (Holtain Ltd., Crosswell, United Kingdom). Age at menarche was derived by 6-monthly history. Body composition was assessed by dual-energy x-ray absorptiometry with a Lunar Prodigy coupled to Lunar software (Lunar Corp., Madison, Wisconsin), as described.⁶

After 4 and 5 years, subcutaneous and visceral fat areas in the abdominal region were assessed by magnetic resonance imaging (MRI) with a multiple-slice MRI 1.5 Tesla scan (Signa LX Echo Speed Plus Excite; General Electric, Milwaukee, Wisconsin), as described.⁶ After 5 years, MRI was also used to assess intrahepatic lipid content (IHLC), by comparing the relative intensity of the liver with that of subcutaneous fat and spleen, assuming that the latter is fat free.¹⁹ The used formula was $IHLC = 100 \times (AI_{liver} - AI_{spleen}) / (AI_{adipose} - AI_{spleen})$, wherein AI is average intensity.¹⁹ All MRI scans were performed by the same operator (blinded to treatment allocation), and all images were analyzed by the same radiologist (also blinded to treatment allocation).

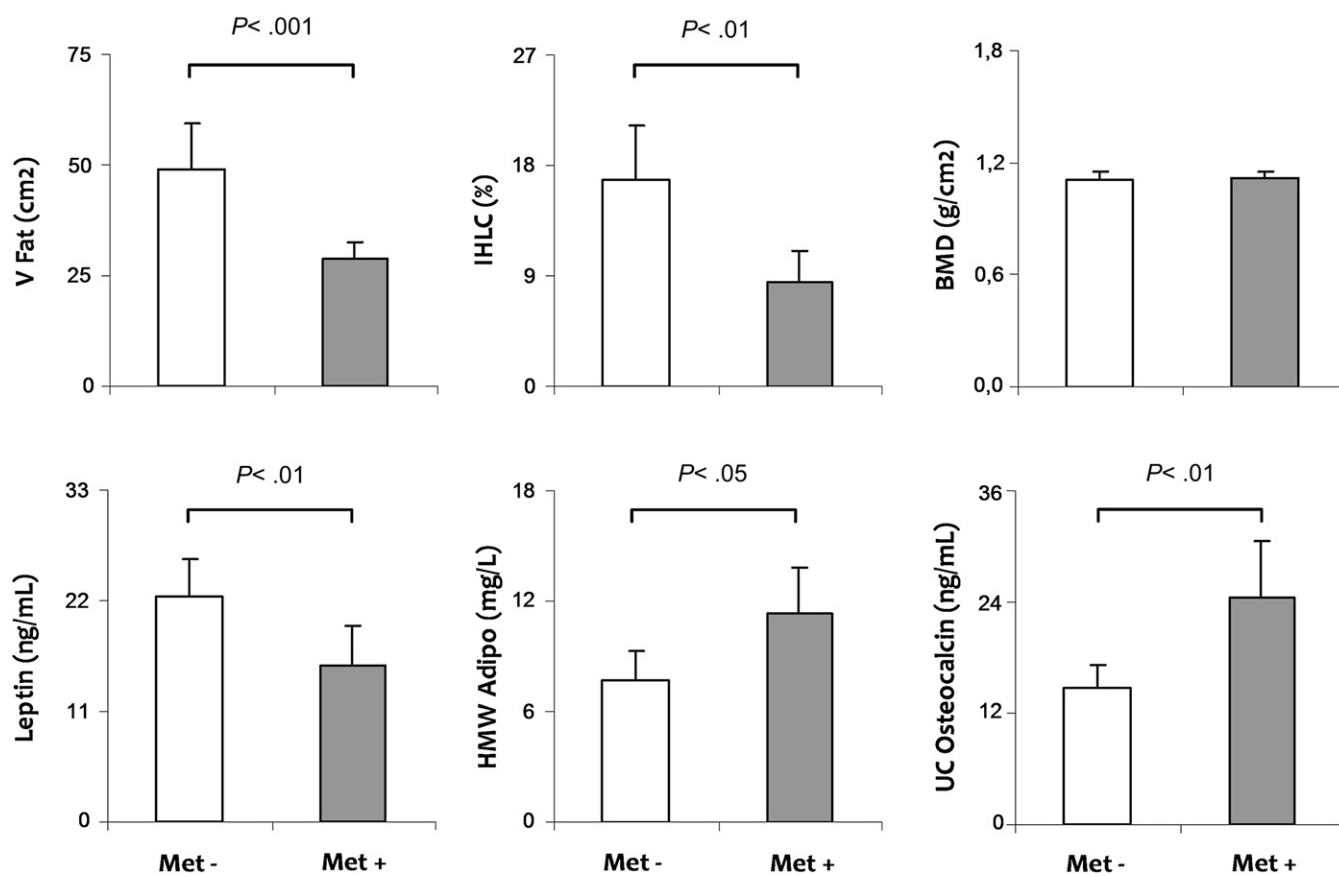


Figure 2. Results after 5 years, for visceral fat (*V Fat*), IHLIC, bone mineral density (*BMD*), leptin, high-molecular-weight adiponectin (*HMW adipo*), and undercarboxylated (*UC*) osteocalcin in prepubertal girls (age ~8 years) with a history of LBW and PP, who were randomized to remain untreated (*Met-*; $n = 19$) or to receive metformin (*Met+*; $n = 19$) for 4 years and who were then followed up for 1 year without intervention. Pubertal metformin treatment was followed by a reduction of visceral and hepatic adiposity, and by a favorable adipokine profile. Plots represent mean and SEM.

Serum glucose was measured by the glucose oxidase method. Serum immunoreactive insulin, SHBG, testosterone, DHEAS, and IGF-1 were assayed by immunochemiluminiscence (Immulite 2000; Diagnostic Products, Los Angeles, California), as described¹⁰; the intraassay and interassay coefficients of variation were between 4% and 8%. Leptin was measured by RIA (Linco, St. Louis, Missouri),²⁰ HMW adiponectin by sandwich ELISA (Linco),²¹ and undercarboxylated osteocalcin by a solid-phase EIA kit (Glu-OC MK-118; Takara Bio, Otsu, Shiga, Japan) on the basis of a sandwich method with 2 monoclonal anti-undercarboxylated osteocalcin antibodies.²² The intraassay and interassay coefficients of variation were 5% and 4.5% for leptin, 2.4% and 5.5% for HMW adiponectin, and 5.2% and 8.3% for osteocalcin, respectively. The samples from randomized subgroups were kept frozen until assay and were assayed concomitantly.

Statistical analyses were performed with SPSS 12.0 (SPSS, Chicago, Illinois). *T*-tests were used to compare the 5-year outcomes between subgroups and general linear model for repeated measures to compare the changes

between subgroups. For uniformity, all results are expressed as mean $\pm$ SEM. The level of significance was set at $P < .05$.

Results

After 5 years, pubertal metformin therapy was associated with less total and abdominal fat (**Figure 1**), with much less visceral and hepatic fat, with lower circulating leptin and with higher levels of HMW adiponectin and undercarboxylated osteocalcin (**Figure 2**). Pubertal metformin therapy was after 5 years also associated with more lean mass and with less androgen excess (**Table**; available at www.jpeds.com).

The 2 subgroups (untreated vs metformin) followed diverging tracks during the 4 years of active treatment¹⁶⁻¹⁸ but followed mostly parallel tracks across year 5. We observed 4 diverging variables: it was only in year 5 that height gain, lean mass, leptinemia, and circulating DHEAS started to diverge. We also noted 1 converging variable: IGF-1 levels in metformin-treated girls rose less than in untreated girls during the 4 years of active study, but they converged toward

control levels in year 5, possibly indicating that the somatotropic axis is among those pathways that escape a persistent resetting by transient metformin therapy.

Pubertal metformin therapy was accompanied by a more normal age at menarche (mean age 11.4 years in 19/19 untreated girls, versus 12.4 years in the 17/19 metformin-treated girls who have so far reached menarche; $P < .0001$), by at least as much height gain (0-5 years) as in the untreated girls, and by a higher growth velocity in year 5 (Table).

Discussion

The sequence of prenatal growth restraint and postnatal excess of weight catch-up is associated with relative hyperinsulinemia, low-grade inflammation, visceral adiposity, and with an amplified adrenarche leading to precocious pubarche, to an early puberty that rapidly progresses to menarche and to polycystic ovary syndrome (often without a polycystic morphology of the ovaries) in adolescence.^{6,7,11,14,18,23-25} Metformin therapy in LBW girls with PP, when initiated postmenarche and given for 1 year, has normalizing effects¹⁰ that, however, persist for less than 6 months beyond metformin withdrawal.¹⁶ Here we report that metformin therapy in LBW girls with PP, when started at age ~ 8 years and given for 4 years across puberty, has broadly normalizing effects,¹⁶⁻¹⁸ most of which seem to persist for at least 1 year beyond stopping metformin intake.

The mechanisms whereby pubertal metformin therapy might partly reset early-life programming remain to be fully delineated. We did not explore the possibility that puberty may serve as a critical window wherein epigenetic settings can be altered, thus leading to a persistent reprogramming of early-life misprogramming. Neither did we explore the possibility that reduced adiposity after 4 years leads to a higher level of physical exercise in the first post-treatment year. An alternative is that long-term metformin therapy upregulates the plasma levels of undercarboxylated osteocalcin,²⁶ and that such upregulation persists beyond metformin intake, thus leading to an endocrine-metabolic profile that fits with the adiponectin-raising and insulin-sensitizing actions of undercarboxylated osteocalcin.^{27,28} A further alternative is that metformin directly downregulates the ovarian estrogen production,²⁹⁻³¹ which is known to be upregulated when LBW is followed by overweight.³² In LBW girls, metformin has pleiotropic effects that can mimic those of physical exercise or caloric restriction, and that may be partly based on metformin's adenosine monophosphate-activated protein kinase-upregulating, insulin-sensitizing and IGF-1 lowering properties.^{15-18,33,34}

The control girls did not receive a placebo over those 4 years. This limitation implies that we can not entirely exclude that the improvements, observed in metformin-treated girls over 5 years, are due to some placebo effect that was not detected in our lifestyle screening over 4 years¹⁸ and that persisted during the off-treatment year. At present, however, each of the 7 randomized, placebo-controlled, metformin tri-

als in nondiabetic children indicates that the effects shown in the present study—particularly those related to body weight, abdominal fat, visceral fat, leptinemia, and/or insulin sensitivity—are attributable to the pharmacologic actions of metformin, rather than to a long-term placebo effect.³⁵⁻⁴¹ ■

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Table. Clinical, endocrine-metabolic, and body composition indexes in prepubertal girls (age ~8 years) with a history of LBW and PP

	Untreated			Metformin		
	Start*	Year 5	Δ 0-5 years	Start*	Year 5 [§]	Δ 0-5 years
Age (y)	8.0 ± 0.2	13.4 ± 0.2	5.4 ± 0.1	7.9 ± 0.2	13.3 ± 0.2	5.4 ± 0.1
Mid-parental height (cm)	161 ± 1	—	—	159 ± 1	—	—
Height (cm)	130 ± 2	157.8 ± 1.8	27.8 ± 0.8	129 ± 2	158.6 ± 1.1	29.7 ± 1.0
Weight (kg)	31 ± 1	57.9 ± 2.5	27.1 ± 2.0	31 ± 1	53.9 ± 1.4	22.6 ± 1.0 [†]
Height velocity (cm/y)	—	1.8 ± 0.4	—	—	3.4 ± 0.5 [‡]	—
Body mass index (z-score)	1.2 ± 0.3	1.6 ± 0.4	0.4 ± 0.3	1.4 ± 0.4	0.6 ± 0.3 [§]	−0.8 ± 0.2
IGF-1 (ng/mL)	215 ± 10	549 ± 27	334 ± 31	197 ± 11	517 ± 27	320 ± 30
Fasting insulin (μU/mL)	8.2 ± 0.6	14.8 ± 1.2	6.5 ± 1.2	8.6 ± 0.9	12.1 ± 1.2	3.5 ± 1.2 [†]
SHBG (μg/dL)	1.6 ± 0.1	0.9 ± 0.1	−0.7 ± 0.1	1.5 ± 0.1	0.9 ± 0.1	−0.6 ± 0.1
DHEAS (μg/dL)	95 ± 9	240 ± 20	145 ± 18	104 ± 10	187 ± 21 [§]	82 ± 15
Androstendione (ng/dL)	90 ± 5	326 ± 20	236 ± 21	98 ± 7	266 ± 12 [§]	168 ± 12
Testosterone (ng/dL)	28 ± 3	66 ± 6	38 ± 7	32 ± 3	51 ± 5 [§]	20 ± 5 [†]
LDL-cholesterol (mg/dL)	102 ± 6	95 ± 5	−7 ± 6	107 ± 7	90 ± 6	−18 ± 4
HDL-cholesterol (mg/dL)	61 ± 3	49 ± 2	−12 ± 3	60 ± 3	54 ± 3	−6 ± 3
Triglycerides (mg/dL)	63 ± 7	85 ± 12	22 ± 10	74 ± 10	65 ± 6	−9 ± 8 [†]
Leptin (ng/mL)	19.5 ± 1.4	22.5 ± 1.8	3.0 ± 2.1	20.7 ± 2.0	15.5 ± 2.1 [‡]	−5.2 ± 2.3
HMW adiponectin (mg/L)	9.1 ± 1.0	7.7 ± 0.8	−1.4 ± 0.9	9.0 ± 1.0	11.3 ± 1.3 [§]	2.4 ± 1.1
Osteocalcin (ng/mL)	68.0 ± 9.3	14.7 ± 1.3	−53.3 ± 9.8	70.1 ± 9.0	24.5 ± 3.1 [‡]	−45.7 ± 9.9
Bone mineral density (g/cm ²)	0.73 ± 0.02	1.1 ± 0.02	0.4 ± 0.02	0.75 ± 0.02	1.1 ± 0.02	0.4 ± 0.02
Lean mass (kg)	19.6 ± 0.5	33.5 ± 1.0	14.0 ± 0.7	19.7 ± 0.7	34.9 ± 0.8 [§]	15.2 ± 0.5
Fat mass (kg)	10.3 ± 0.9	21.9 ± 0.8	11.5 ± 1.3	10.8 ± 1.0	17.2 ± 1.1 [§]	6.3 ± 0.9
Abdominal fat (kg)	2.8 ± 0.3	6.7 ± 0.4	3.9 ± 0.4	3.0 ± 0.4	4.9 ± 0.3 [‡]	1.9 ± 0.3 [¶]
Subcutaneous fat (cm ²)	—	136 ± 16	—	—	135 ± 14	—
Visceral fat (cm ²)	—	49 ± 5	—	—	29 ± 2 [#]	—
Visceral-to-subcutaneous fat	—	0.40 ± 0.03	—	—	0.24 ± 0.02 ^{**}	—
Intrahepatic lipid content (%)	—	16.8 ± 2.2	—	—	8.5 ± 1.3 [‡]	—

LDL, Low-density lipoprotein; HDL, high-density lipoprotein.

Girls were randomized to remain untreated (n = 19) or to receive metformin (n = 19) for 4 years; all girls were then followed up over 1 year without intervention, for a total study duration of 5 years. Values are mean ± SEM. To convert units to SI, multiply the concentrations of testosterone by 0.03467; those of DHEAS by 0.02714; divide the concentrations of SHBG by 0.0288; those of triglycerides by 88.5, and those of HDL-cholesterol and LDL-cholesterol by 38.7.

*No significant differences between randomized subgroups at start.

†P < .05 for 0-5 years change (Δ) vs untreated.

‡P ≤ .01 vs untreated after 5 years.

§P < .05 vs untreated after 5 years.

||P ≤ .01 for 0-5 years change (Δ) vs untreated.

¶P ≤ .001 for 0-5 years change (Δ) vs untreated.

#P ≤ .001 vs untreated after 5 years.

**P ≤ .0001 vs untreated after 5 years.