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Pubertal adiposity after fetal growth restraint: toward a calorie restriction mimetic approach

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Abstract

Randomized studies in early-maturing (P2 <8 years, B2 between 8 and 9 years), low–birth weight girls (N = 60) show that calorie restriction mimetic therapy with metformin for 3 years is accompanied by a strikingly leaner body composition (on average, 5.2 kg less gain of fat; 1.6 kg more gain of lean mass; $P < .0001$).

1. Introduction

Among the girls with precocious pubarche (PP; pubic hair or Tanner P2 <8 years) or with early-normal puberty (ENP; breast budding or Tanner B2 between 8 and 9 years), those with a low birth weight (LBW) are at risk for a rapidly progressive puberty, which is thought to be driven by hyperinsulinemia and by a high fraction of body fat (adiposity), even in the absence of obesity [1-3].

Metformin is an insulin-sensitizing and a calorie restriction mimetic agent [4,5], and since 2002 has been known to have normalizing effects on the endocrine-metabolic state and on the adiposity of postmenarcheal LBW adolescents [6].

A first study in LBW-ENP girls suggested that metformin could reduce body adiposity and delay the progression of puberty [3]. The 2-year results of another study in LBW-PP girls showed that metformin could also delay the onset of puberty [7]. We compiled the results of the first study and the novel 3-year results of the latter study into a first analysis of metformin effects over 3 years in early-maturing LBW girls.

2. Study population and methods

2.1. Subjects and study design

2.1.1. LBW-PP girls

As described [7], the inclusion criteria were as follows: (1) weight <2.9 kg at term birth (38-41 weeks) or below −1 standard deviation score for gestational age at preterm birth (33-37 weeks); (2) PP due to exaggerated adrenarche; (3) body mass index (BMI) <22 kg/m^2; and (4) prepuberty (Tanner B1).

The cohort consisted of 38 LBW-PP girls in 2 subpopulations of 19 girls [7]. Birth weight was 2.4 ± 0.1 kg after 39 ± 0.4 weeks; age at PP diagnosis, 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/m^2; dehydroepiandrosterone sulfate (DHEAS) at PP diagnosis, 102 ± 6 μg/dL; and post–adrenocorticotropic hormone 17-hydroxyprogesterone, 274 ± 16 ng/dL.

Girls were randomly assigned to remain untreated or to receive metformin, once daily, at dinner time (425 mg/d for 2 years, 850 mg/d in year 3). Clinical examination with

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pubertal staging was performed every 6 months; assessment of serum insulin, fasting blood glucose, sex hormone–binding globulin (SHBG), testosterone, DHEAS, lipid profile, and body composition were each performed every 6 months for 2 years, and yearly thereafter. One investigator (LI) assessed breast development by palpation.

2.1.2. LBW-ENP girls

As described [3], inclusion criteria were as follows: (1) birth weight below −1.5 standard deviation score; (2) puberty start (B2) between 8.0 and 9.0 years, and less than 1 year before study start; (3) height ≥1 SD above midparental height SD; (4) bone age ≥1 year above chronological age; and (5) central and progressive puberty, as judged by gonadotropin-releasing hormone (GnRH) agonist test and by pubertal dimensions of the internal genitalia on ultrasound examination.

The cohort consisted of 22 girls [3]. Birth weight was 2.4 ± 0.1 kg after 40 ± 0.3 weeks; age at start of B2, 8.6 ± 0.1 years; age at study start, 9.1 ± 0.1 years; bone age, 10.4 ± 0.1 years; height, 139.3 ± 1.3 cm; weight 40.0 ± 1.2 kg; BMI 20.6 ± 1.5 kg/m^2.

Girls were randomized to remain untreated (n = 12) or receive metformin (n = 10, 850 mg) once daily, at dinner time, for 3 years; pubertal growth, body composition, uterine and ovarian size, and endocrine-metabolic markers were assessed every 6 months.

2.2. Ethics

Both studies were conducted in Barcelona, without support from industry, after approval by the Institutional Review Board of Sant Joan University Hospital, and after informed consent from parents and assent from minors. Study registration numbers are ISRCTN84749320 (LBW-PP) and ISRCTN06805028 (LBW-ENP).

2.3. Body composition

As described [3,7], body composition was assessed by absorptiometry with a Lunar Prodigy coupled to Lunar software (Lunar, Madison, WI). Total bone mineral content was measured at L2 through L4 level with a Lunar DPX-L; bone mineral content values were corrected for surface area and converted into bone mineral density values.

Table 1
Clinical, endocrine-metabolic, and body composition indices in girls with a combined history of LBW and either PP or early puberty

	Reference[a] at start	All at start	Untreated			Metformin		
			Start[b]	3 y	Δ 0-3 y	Start[b]	3 y	Δ 0-3 y
Age at randomization (y)	–	8.4 ± 0.1	8.5 ± 0.1	11.6 ± 0.2[e]	3.1 ± 0.1	8.3 ± 0.2	11.5 ± 0.2[h]	3.2 ± 0.1
Tanner breast (stage)	–	1.4 ± 0.1	1.4 ± 0.1	4.6 ± 0.1[e]	3.2 ± 0.1	1.4 ± 0.2	3.8 ± 0.2[e]	2.5 ± 0.2[h]
Weight (kg)	–	34.3 ± 0.9	33.9 ± 1.2	50.7 ± 1.6[e]	16.8 ± 1.0	34.8 ± 1.4	48.6 ± 1.4[h]	13.8 ± 0.5[g]
Height (cm)	–	133 ± 1	133 ± 2	152 ± 1[e]	19 ± 1	133 ± 1.6	153 ± 2[h]	20 ± 1
BMI (kg/m^2)	17.7 ± 0.4	19.2 ± 0.3	18.9 ± 0.4	21.7 ± 0.5[e]	2.8 ± 0.3	19.5 ± 0.5	20.7 ± 0.4[h]	1.2 ± 0.2[h]
Fasting insulin (μU/mL)	6.6 ± 0.7	10.2 ± 0.7	9.6 ± 0.8	16.0 ± 1.0[e]	6.4 ± 1.1	10.5 ± 1.1	12.5 ± 1.0[c]	2.0 ± 1.3[g]
HOMA-IR	1.0 ± 0.1	2.1 ± 0.1	2.0 ± 0.2	3.8 ± 0.3[e]	1.8 ± 0.3	2.2 ± 0.2	2.9 ± 0.2[d]	0.7 ± 0.3[g]
SHBG (μg/dL)	3.6 ± 0.1	1.4 ± 0.1	1.5 ± 0.1	1.0 ± 0.1[e]	−0.5 ± 0.1	1.3 ± 0.1	1.2 ± 0.1	−0.2 ± 0.1[g]
Testosterone (ng/dL)	17 ± 2	32 ± 1	32 ± 2	46 ± 2[d]	14 ± 2	32 ± 2	35 ± 2	2 ± 2[f]
LDL cholesterol (ng/mL)	81 ± 4	101 ± 3	100 ± 5	104 ± 4	4 ± 4	107 ± 7	98 ± 5[c]	−9 ± 4[f]
HDL cholesterol (ng/mL)	66 ± 2	60 ± 2	61 ± 3	49 ± 2[e]	−12 ± 2	60 ± 3	60 ± 1	0.0 ± 2[h]
Triglycerides (ng/mL)	53 ± 2	71 ± 8	64 ± 7	73 ± 10[d]	9 ± 9	80 ± 10	71 ± 9	−9 ± 8[g]
Fat mass (kg)	6.4 ± 0.6	11.4 ± 0.6	10.9 ± 0.8	19.4 ± 1.1[e]	8.5 ± 0.6	11.9 ± 0.8	15.2 ± 0.8[e]	3.3 ± 0.4[i]
Abdominal fat mass (kg)	1.2 ± 0.2	3.4 ± 0.2	3.2 ± 0.3	5.8 ± 0.3[e]	2.6 ± 0.2	3.6 ± 0.4	4.2 ± 0.3[d]	0.6 ± 0.2[i]
Lean mass (kg)	20.2 ± 1.0	21.9 ± 0.6	21.7 ± 0.8	29.2 ± 0.8[e]	7.5 ± 0.5	22.1 ± 0.8	31.2 ± 1.0[e]	9.1 ± 0.4[g]
BMD (g/cm^2)	0.71 ± 0.04	0.77 ± 0.01	0.76 ± 0.02	0.97 ± 0.03[e]	0.22 ± 0.02	0.78 ± 0.02	0.99 ± 0.03[e]	0.22 ± 0.02

Girls were randomized to remain untreated (n = 31) or to receive treatment with metformin (n = 29) for 3 years.

Values are mean ± SEM. To convert units to SI, multiply the concentrations of testosterone by 0.03467, those of androstenedione by 0.0349, and those of DHEAS by 0.02714; divide the concentrations of SHBG by 0.0288; those of triglycerides by 88.5, and those of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol by 38.7. HOMA-IR indicates homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMD, bone mineral density.

[a] Nonsymptomatic prepubertal girls (n = 24 for endocrine-metabolic variables; age, 8.3 ± 0.3 years; n = 13 for body composition; age, 8.4 ± 0.4 years).

[b] No significant differences between randomized subgroups at start.

[c] $P < .05$.

[d] $P \leq .01$.

[e] $P \leq .0001$ vs start.

[f] $P < .05$.

[g] $P \leq .01$.

[h] $P \leq .001$.

[i] $P \leq .0001$ for 0- to 3-year change (Δ) vs untreated.

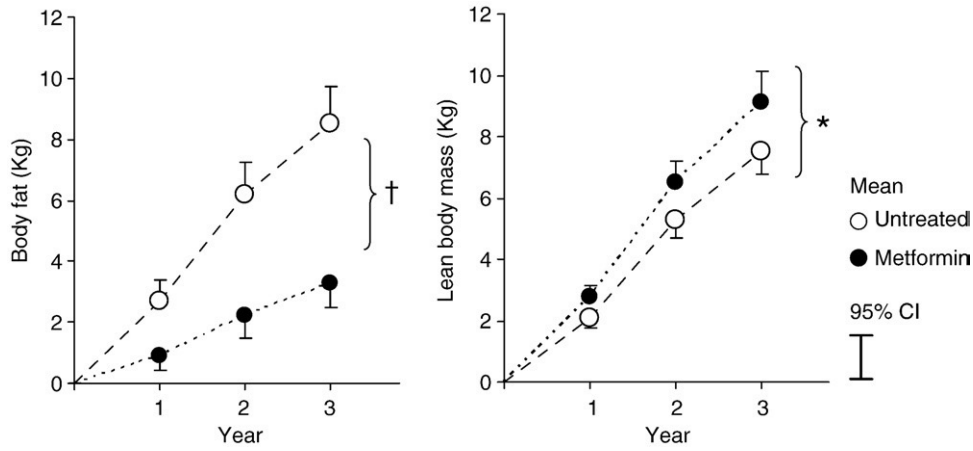

Fig. 1. Gain of body fat and lean mass in early-maturing LBW girls (N = 60) who were randomized to remain untreated (n = 31) or to receive metformin (n = 29) for 3 years. Metformin therapy is accompanied by less gain of fat and by more gain of lean mass. Means ± 95% confidence interval are shown. *$P < .05$ and †$P < .001$ for longitudinal differences between subgroups.

2.4. Hormone assays and statistics

Serum glucose was measured by the glucose oxidase method. Serum insulin, SHBG, testosterone, DHEAS, androstenedione, 17-hydroxyprogesterone, and lipid profile were assayed as described [3,7]. Fasting insulin sensitivity was estimated by homeostasis model assessment (HOMA-CIGMA Calculator program version 2.00, Diabetes Research Laboratory, Oxford, UK).

Two-sided *t* tests allowed for comparisons within and between subgroups. Repeated-measures analysis of variance tested the longitudinal differences between subgroups. Results are expressed as mean ± SEM. Statistical significance was set at $P < .05$.

3. Results

Metformin effects were similar in LBW-PP and LBW-ENP girls; Table 1 shows the compiled data over 3 years. Metformin therapy was accompanied by a strikingly leaner body composition (Fig. 1).

4. Discussion

A consistent hallmark of girls with idiopathic variants of early sexual maturation is that they are adipose (ie, have a high fat fraction), even when not obese [8,9]. Another robust finding in those girls is that GnRH agonist therapy aggravates their adiposity, suggesting that a selective silencing of their gonadotropic axis fails to revert their endocrine-metabolic settings toward normal [9,10]. The early-maturing LBW girls in the present analysis were also adipose, and metformin reverted their adiposity toward the norm. Thus, there starts to be a rationale to use metformin as an adjuvant to GnRH agonist—if not as a prime therapy—in early-maturing LBW girls. It is so far unknown whether metformin has similar benefits in early-maturing girls without LBW.

The mechanisms underpinning the efficacy of metformin in early-maturing LBW girls are still poorly understood. Metformin, through activation of 5'-AMP–activated protein kinase, improves insulin sensitivity in muscle and liver, decreases hepatic glucose production and lipid synthesis, increases oxidation of fatty acids and peripheral glucose utilization, and has positive effects on insulin receptor expression and tyrosine kinase activity [4,11]. In addition, metformin has direct effects on steroidogenesis in ovarian granulosa and theca cells [12]. A new perspective on metformin's hepatic actions emerged when microarray studies revealed that metformin is capable of inducing a hepatic gene expression pattern that closely mimics the profile of calorie restriction [5].

In conclusion, an analysis of 3-year results from 60 LBW girls indicates that calorie restriction mimetic therapy with metformin, if started shortly after the early appearance of pubic hair or breast budding, is accompanied by a strikingly less adipose body composition.

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