Abstract

OBJECTIVES: Metformin has shown its effectiveness in treating obesity in adults. However, little research has been conducted in children, with a lack of attention on pubertal status. The objectives were to determine whether oral metformin treatment reduces BMI z score, cardiovascular risk, and inflammation biomarkers in children who are obese depending on pubertal stage and sex.

METHODS: This was a randomized, prospective, double-blind, placebo-controlled, multicenter trial, stratified according to pubertal stage and sex, conducted at 4 Spanish clinical hospitals. Eighty prepubertal and 80 pubertal nondiabetic children who were obese aged 7 to 14 years with a BMI >95th percentiles were recruited. The intervention included 1 g/d of metformin versus placebo for 6 months. The primary outcome was a reduction in BMI z score. Secondary outcomes comprised insulin resistance, cardiovascular risk, and inflammation biomarkers.

RESULTS: A total of 140 children completed the study (72 boys). Metformin decreased the BMI z score versus placebo in the prepubertal group (−0.8 and −0.6, respectively; difference, 0.2; P = .04). Significant increments were observed in prepubertal children treated with metformin versus placebo recipients in the quantitative insulin sensitivity check index (0.010 and −0.007; difference, 0.017; P = .01) and the adiponectin–leptin ratio (0.96 and 0.15; difference, 0.81; P = .01) and declines in interferon-γ (−5.6 and 0; difference, 5.6; P = .02) and total plasminogen activator inhibitor-1 (−1.7 and 2.4; difference, 4.1; P = .04). No serious adverse effects were reported.

CONCLUSIONS: Metformin decreased the BMI z score and improved inflammatory and cardiovascular-related obesity parameters in prepubertal children but not in pubertal children. Hence, the differential response according to puberty might be related to the dose of metformin per kilogram of weight. Further investigations are necessary.
Overweight and obesity in children are the most challenging health problems to address. Obesity plays an important pathophysiologic role in the development of insulin resistance, dyslipidemia, and hypertension, leading to type 2 diabetes mellitus (T2DM) and a risk of early cardiovascular disease. For pediatric patients, several investigations have confirmed that an intensive lifestyle intervention can increase weight loss and insulin sensitivity and reduce the risk of developing T2DM. Nevertheless, a single-strategy lifestyle intervention is not always effective. In addition, efforts have been made to identify effective and safe drugs to manage pediatric obesity. Metformin is an oral antihyperglycemic agent approved by the US Food Drug Administration to treat T2DM in adults and children aged >10 years; it is considered a first-line agent in T2DM by the European Medicines Agency. Significant weight loss induced by metformin has been shown in adults who are obese with or without T2DM. Metformin also produced a decrease in the cardiovascular risk profile and inflammatory biomarkers.

Nevertheless, evidence regarding the effects of metformin in pediatric obesity is scarce. According to a systematic review and meta-analysis, a reduction in BMI due to metformin compared with the effects of lifestyle interventions alone from 6 to 12 months has been reported in children who are obese. Seven studies have evaluated the effects of metformin (1000–2000 mg/d for 3–6 months) on such conditions related to obesity in children and/or adolescents who are obese, with some promising results obtained. However, randomized controlled trials (RCTs) on this topic did not show an adequate and separate distribution in the study design according to prepubertal and pubertal children. Puberty might act as a potential modifier on the effect of metformin in childhood. Thus, it seems useful to stratify randomization according to Tanner stage and sex to avoid large imbalances between groups in linear growth velocity and other factors associated with pubertal maturation that may affect changes in BMI.

We therefore designed an RCT to determine whether metformin would have an effect on reducing the BMI z score and improving cardiovascular and inflammatory risk biomarkers in children who are obese and to assess whether this effect differed depending on pubertal stage and sex.

### METHODS

#### Study Design

The study was a multicenter investigation, stratified according to sex and pubertal status (40 prepubertal girls, 40 prepubertal boys, 40 pubertal girls, and 40 pubertal boys). Pubertal stage was determined according to Tanner criteria (standards for pubic hair and genitalia growth in boys; standards for breast and pubic hair development in girls) through a physical examination by the pediatric endocrinologists at the beginning and the end of the study. This randomized, double-blind, placebo-controlled trial was homogeneously conducted at 4 Spanish clinical hospitals, as previously described. Children were randomly assigned to receive either metformin or placebo for 6 months. Details of the trial protocol and ethics committees have been previously published in *Trials*. The Consolidated Standards of Reporting Trials statement has been considered in the report on study design and results, as well as in the abstract and flow diagram.

### Intervention and Participants

The study subjects comprised 160 patients referred from the Pediatric Endocrinology Unit of the corresponding study centers. Children were invited to participate according to the inclusion criteria described in Table 1. The data are collected in the pediatric outpatient clinics by dietitians. All participants were provided with standardized healthy lifestyle advice at the beginning of a 1-on-1 session according to recommendations for food consumption frequency following the Mediterranean diet criteria and the practice of physical activity based on the AECOSAN NAOS Strategy’s NAOS Pyramid (Ministry of Health of the Spanish Government). The data and samples were codified according to each center and subsequently centralized at the Institute of Nutrition and Food Technology “José Mataix” in Granada, Spain.

The participants were assigned to receive metformin or placebo in

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>BMI greater than the 95th percentile based on the standards of Cole et al</td>
<td>Does not meet the established age</td>
</tr>
<tr>
<td>Age 7–14 y</td>
<td>Any previous underlying disease</td>
</tr>
<tr>
<td>No underlying disease or a history of pathology</td>
<td>Use of medication with metabolic side effects, such as diuretics, β-blockers, β-adrenergics, or corticoids</td>
</tr>
<tr>
<td>No medical treatment regarding weight control in the previous 12 mo</td>
<td>Cases of monogenic obesity</td>
</tr>
<tr>
<td>No participation in a previous trial</td>
<td>Children subjected to long periods of rest</td>
</tr>
<tr>
<td>—</td>
<td>Did not sign the informed consent</td>
</tr>
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</table>
both of which have been validated and normalized. The data collected in the lifestyle habits questionnaires were evaluated according to the healthy lifestyle/diet (HLD) index described by Manios et al. to ensure routine quality estimation. The total score on the HLD index ranges from 0 to 48, with higher scores indicating “healthier” dietary/lifestyle patterns. Based on this scoring, they considered 3 groups according to tertiles of the HLD index: unhealthy dietary/diet pattern, scores ranging from 1 to 16; moderately HLD pattern, scores ranging from 17 to 32; and HLD pattern, scores ranging from 33 to 48.

**Sample Size**

The sample size was calculated based on BMI as the main outcome, the SD being 2.29 according to the tables of Cole et al., and an expected minimum difference of 2 points of BMI. With an α error of 0.05, a β error of 0.20, and an estimated follow-up loss (dropout) of 20%, 4 groups in total were planned for the study: 2 groups of children who were obese (prepubertal and pubertal) treated with metformin and 2 groups of children who were obese (prepubertal and pubertal) who received placebo. There is a requirement of at least 40 patients per group (x4 groups = 160 children).

**Statistical Analysis**

Data were analyzed by using SPSS software version 22 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY). All values are expressed as mean ± SEM. Variables that were not normally distributed were log-transformed for analysis, and/or values with ±2 SD of the mean were removed (without achieving values loss from samples of up to 15%). However, the data are presented as untransformed values to ensure a clear understanding. Differences at baseline per experimental group in each pubertal stage or sex were assessed by using Student’s t test or the Mann-Whitney U test if the variables were not normally distributed. The data associated with the subjects who dropped out were subsequently excluded from the statistical analysis.

A general linear model for repeated measures was used to determine the outcome changes from baseline to 6 months according to treatment of separated groups of pubertal status (prepubertal and pubertal) and sex (boys and girls). The specific differences between the treatments were assessed by using post hoc Bonferroni tests. The fixed effects included were sex or pubertal stage.
dropped out. Subjects who dropped out were mainly lost to incomplete follow-up (did not attend at the last visit) and/or they were no longer interested in the study. The baseline demographic, clinical, and biochemical characteristics are summarized in Supplemental Table 4. Children presented with normal fasting blood glucose concentrations according to the International Society for Pediatric and Adolescent Diabetes. In addition, differences at baseline between the intervention groups were found for leptin and γ-glutamyltransferase concentrations in prepubertal participants and for BMI, waist circumference, oxidized low-density lipoprotein, creatinine, and urea in pubertal participants. Regarding sex, higher values were observed at baseline in the placebo group compared with the metformin group for BMI (30.2 ± 0.7 vs 28.0 ± 0.6; P = .04) and leptin (15.07 ± 1.0 µg/L vs 10.8 ± 1.0 µg/L; P = .003) in boys, whereas soluble vascular adhesion molecule-1 was lower in girls in the placebo group (696 ± 33 µg/L vs 790 ± 33 µg/L; P = .05).

Anthropometry, Body Composition, and Lifestyle Monitoring

Unlike placebo, metformin treatment decreased the BMI z score (P = .04) in the prepubertal group. Moreover, based on a binary logistic regression, the BMI z score was independently associated with metformin treatment (odds ratio, 0.18 [95% confidence interval, 0.050–0.636]; P = .01); therefore, the 6-month metformin intervention led to a reduction in BMI z score in the prepubertal group. Conversely, the other anthropometric and body composition parameters revealed no significant differences between the interventions at 6 months in any pubertal group (Table 2). No differences were found in the impact of metformin according to the pubertal stage when the interaction time × treatment × puberty was applied to the entire population (P = .41). Concerning sex, there were no differential effects in boys compared with girls (data not shown).

All subjects kept a moderately HLD pattern (second tertile, ranging from 17 to 32 values of HLD index) at all study times. In addition, we observed no difference in behavior for the experimental groups according to pubertal stage and sex across the study.

Glucose, Insulin Sensitivity, and Lipid Metabolism

Metformin treatment significantly increased the QUICKI in prepubertal children compared with placebo (P = .01) (Table 2); no differences were observed in the impact of metformin according to the pubertal stage when the interaction time × treatment × puberty was applied to the entire population (P = .47). There was no evidence of significant differences in other insulin sensitivity markers at 6 months in either the prepubertal or pubertal group, regardless of treatment. The lipid profile did not change throughout the intervention in any treatment group. Data stratified according to sex exhibited no differences between treatments (data not shown).

Inflammation and Cardiovascular Risk Biomarkers

After the intervention, the prepubertal group exhibited decreased IFN-γ and tPAI-1 concentrations in patients in the metformin group compared with those receiving placebo (P = .02; P = .04, respectively) (Table 3). Leptin and adiponectin concentrations did not change over time in either group; however, the ALR increased in prepubertal children after metformin treatment versus placebo (P = .01). Furthermore, pubertal children did not show any changes at the end of the trial in the metformin group versus the placebo group.

Neither ALR, tPAI-1, nor IFN-γ exhibited a different impact of metformin according to the pubertal
stage when the interaction time × treatment × puberty was applied to all the population (P = .07; P = .14; P = .06, respectively).

Regarding sex, boys had an increased ALR after metformin treatment versus placebo (baseline, 1.0 ± 0.1 to 6 months 1.7 ± 0.2 by metformin vs baseline 0.7 ± 0.09 to 6 months 0.9 ± 0.2 by placebo, P = .04), but girls only showed a trend (0.7 ± 0.09 to 1.2 ± 0.1 by metformin vs 0.7 ± 0.09 to 0.9 ± 0.1 by placebo; P = .08). For the remaining outcomes, we observed no differential effects in either sex (data not shown).

Safety, Adherence, and Doses
Metformin was generally well tolerated. None of the subjects had to stop the intervention because of serious adverse events. Both experimental groups reported having diarrhea (13% in the metformin group, 9% in the placebo group). Lactic acidosis was not reported in any participant. There were no significantly different changes in any safety parameters between the metformin and placebo groups. The clinical signs did not differ at the end of the intervention in any treatment group.

Adherence was measured by using the following formula: ([pills ingested − pills returned]/pills predicted) × 100. Good adherence to treatment was reported in most participants (89% ± 1%). In terms of doses, all patients received 1 g/d of medication, independent of weight. Considering the different effects of metformin according to pubertal stage, we considered it appropriate to calculate the doses per body weight of each patient. Thus, prepubertal children took 19.6 ± 0.74 mg metformin/kg body weight versus 13.4 ± 0.38 mg/kg taken by the pubertal children (P < .001).

DISCUSSION
In the present RCT, we recorded a significant reduction in BMI z score after 6 months exclusively in prepubertal children who were obese treated with 1 g/d of metformin, even with no significant improvement in lifestyle according to the HLD index of Manios et al. Metformin has previously been found to be efficacious in childhood obesity, especially in reducing BMI z score.
#### TABLE 2  Changes in Anthropometry, Body Composition, Glucose, Insulin Sensitivity, and Lipid Metabolism in Children Who Are Obese According to Pubertal Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prepubertal ( Tanner Stage I )</th>
<th>Pubertal ( Tanner Stages II–V )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Metformin</td>
</tr>
<tr>
<td></td>
<td>(n = 40)</td>
<td>(n = 34)</td>
</tr>
<tr>
<td>Adiponectin, mg/L</td>
<td>12.4 ± 1.2</td>
<td>13.5 ± 1.3</td>
</tr>
<tr>
<td>Leptin, µg/L</td>
<td>15.8 ± 1.1</td>
<td>14.5 ± 1.2</td>
</tr>
<tr>
<td>ALR</td>
<td>0.91 ± 0.1</td>
<td>1.10 ± 0.2</td>
</tr>
<tr>
<td>Resistin, µg/L</td>
<td>10.7 ± 0.9</td>
<td>12.8 ± 1.1</td>
</tr>
<tr>
<td>IFN-γ, ng/L</td>
<td>11.3 ± 2.0</td>
<td>11.3 ± 1.6</td>
</tr>
<tr>
<td>IL-6, ng/L</td>
<td>2.8 ± 0.4</td>
<td>2.7 ± 0.4</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>3.6 ± 0.4</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td>MCP-1, ng/L</td>
<td>2014.1 ± 82.2</td>
<td>1821.8 ± 111.1</td>
</tr>
<tr>
<td>TNF-α, ng/L</td>
<td>8.7 ± 0.6</td>
<td>8.2 ± 0.5</td>
</tr>
<tr>
<td>VEGF, ng/L</td>
<td>13.9 ± 12.0</td>
<td>134.1 ± 12.6</td>
</tr>
<tr>
<td>MPO, µg/L</td>
<td>142.0 ± 36.9</td>
<td>84.3 ± 12.8</td>
</tr>
<tr>
<td>sICAM-1, µg/L</td>
<td>108.7 ± 7.9</td>
<td>90.2 ± 6.5</td>
</tr>
<tr>
<td>sVCAM-1, µg/L</td>
<td>723.5 ± 41.9</td>
<td>683.0 ± 37.9</td>
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<tr>
<td>tPAI-1, µg/L</td>
<td>18.8 ± 1.8</td>
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<tr>
<td>Ox-LDL, µmol/L</td>
<td>3792.7 ± 963</td>
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</tr>
</tbody>
</table>

#### TABLE 3  Changes in Adipokine Levels, Biomarkers of Inflammation, and Cardiovascular Risk in Children Who Are Obese According to Pubertal Status

<table>
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A lack of effect of metformin in the pubertal children who were obese might be related to the lower doses used for these subjects (milligrams of metformin per kilograms of body weight), providing dose-dependent efficacy according to body weight. Reviewing the literature, only Mauras et al.41 divided metformin doses into 1000 mg/d for those aged <12 years and 2000 mg/d for those aged ≥2 years; however, their sample size was small, and no differential responses were observed according to the pubertal stage. Nevertheless, we cannot exclude the fact that the failure of a metformin effect in pubertal children could also be due to the physiologic and hormonal changes in that stage. Indeed, puberty is associated with a marked decrease in insulin sensitivity,33 and an insulin-sensitizing therapy would therefore have to be increased proportionately to observe a similar effect in prepubertal children. Accordingly, future RCTs should consider higher doses of metformin for adolescents to obtain a beneficial effect, taking into account the maximum dosing described for youngsters aged 10 to 16 years (2000 mg/d).34

Regarding the lipid profiles, no significant changes occurred in any pubertal group. Three studies have shown an improvement in some lipid parameters in pubertal subjects who are obese.17,35,36 However, no changes were observed compared with the placebo intervention by many other studies in patients both prepubertal and pubertal who were obese.18,21,22,30,37 nor were there any changes in pubertal population only.16,20,29,32 Hence, the evidence is still unclear and seems to depend on the presence/absence of dyslipidemia.38 Furthermore, metformin is considered as an insulin sensitizer, with its pleiotropic actions, and it exerts protective effects on multiple organs, mainly in insulin-targeted tissues such as liver, muscle, and adipose tissues.39 In the current study, QUICKI, considered for years as an optimal method of determining insulin sensitivity in subjects who are obese, increased only in the prepubertal children. One previous RCT assessed the changes in QUICKI according to a metformin intervention for 6 months in an experimental group comprising both prepubertal and pubertal children who were obese, but no effects were obtained.22 Moreover, a significant increase has only been shown to date in pubertal children who are obese.32,36 A significant improvement in the ALR was observed in the prepubertal children after taking metformin. The ALR is considered a potential surrogate marker for cardiometabolic disease.40 Similar results have been reported by previous investigators in children22 and adolescents who are obese.17,22 However, we found no effects of metformin on plasma adipokine levels. In reviewing previous studies of subjects who are obese aged 4 to 19 years, levels of adiponectin did not change during the metformin intervention compared with placebo,16,17,19,20,22 neither did leptin levels, which were found to be decreased only in 2 studies.32,35 Freemark and Bursey32 reported a decrease in pubertal girls who were obese but not in their male peers.

A variety of proinflammatory mediators associated with cardiometabolic dysfunction are known to be influenced by childhood obesity.22 We have reported for the first time a decline in INF-γ plasma concentrations after metformin treatment over 6 months in prepubertal children who are obese only. There are no studies to date in humans that assessed changes in INF-γ in subjects who are obese. However, it has been reported that metformin exerted its immunosuppressive effect by inhibiting the expression of proinflammatory mediators as IFN-γ both in a macrophage cell line (RAW267.4) and in animal models of multiple sclerosis.41 This finding may be interesting enough to warrant investigation of other actions of metformin pathways. Similarly, tPAI-1 is a principal physiologic inhibitor of fibrinolysis and a relevant marker of inflammation and prothrombosis.42 Thus far, only Mauras et al.41 have evaluated the effects of metformin on tPAI-1 concentrations, and they observed no changes by metformin and no differences according to pubertal stage. The current RCT is the first study to report an influence of metformin on tPAI-1 reduction in pediatric patients who are obese and only in the prepubertal group. CRP was not modified in the current study in either pubertal group after treatment. Different investigators have evaluated this inflammatory biomarker after metformin interventions, but none of them found changes.16,19–22 Another well-known inflammation biomarker, TNF-α, has been studied only in 2 RCTs similar to ours.19,20

the most appropriate and precise internationally accepted body mass parameter for children.26 Previous investigators have reported similar effects of 1500 to 2000 mg/d after 6 months in prepubertal and pubertal children who are obese.18,22,28 In the current study, we found no significant change concerning BMI z score in pubertal children who were obese, similar to findings from some RCTs in this population29–31 but different from other RCTs.17,32 The diverse results found in the present RCT illustrate the importance of considering puberty in intervention studies of metformin in children who are obese. None of the previous studies used a study design to allow observing a differential response according to pubertal status separately.
Only Evia-Viscarra et al\(^9\) observed changes in the variances of serum TNF-α concentration over 3 months in pubertal children who are obese. In terms of the other cardiovascular risk and inflammatory biomarkers, they had not been analyzed to date in children who are obese. However, changes in these biomarkers were not found in the current study. Evidence regarding some of these biomarkers has only been achieved in the adult population.\(^7\)–\(^14\) Thus, more studies are needed to elucidate the effects of metformin on inflammatory biomarkers in the early onset of obesity.

Our study has several limitations, including the difficulty in assessing treatment compliance by using pill count, as well as lifestyle changes in the children. In addition, although the index proposed by Manios et al\(^27\) has been validated for primary school children and was carefully revised, it did not include the intake of some routine foods in the Spanish diet (eg, olive oil), which may influence dietary habits. Furthermore, we controlled for medication taken by monitoring the delivery and return of pill bottles; however, we are aware that this strategy does not ensure accuracy regarding information on intervention compliance.

**CONCLUSIONS**

The onset of childhood obesity may begin early in life. This fact clearly has important implications for the future development of cardiovascular disease in children who are obese and in young people. Better pharmacologic strategies are needed to reduce cardiovascular risk in this population. In the present RCT, prepubertal children had a decreased BMI z score and improvements in other parameters related to obesity after undergoing metformin treatment for 6 months, but pubertal children did not. Hence, puberty is an important physiologic stage that plays a key role in the differential response to metformin that should be explored further, particularly in terms of the dose–effect relationships.

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**ABBREVIATIONS**

ALR: adiponectin–leptin ratio  
CV: coefficient of variation  
HLD: healthy lifestyle/diet  
IFN-γ: interferon-γ  
PAI-1: plasminogen activator inhibitor-1  
QUICKI: quantitative insulin sensitivity check index  
RCT: randomized controlled trial  
T2DM: type 2 diabetes mellitus  
TNF-α: tumor necrosis factor α
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