Systematic Review of Metformin Use in Obese Nondiabetic Children and Adolescents

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Key Words

Metformin · Obesity · Children · Insulin resistance

Abstract

Objective: Childhood obesity has become epidemic and has been accompanied by an increase in prevalence of type 2 diabetes (T2DM) in youth. Addressing obesity and insulin resistance by drug treatment represents a rational strategy for the prevention of T2DM. A systematic review was performed to evaluate the effectiveness of metformin in reducing weight and ameliorating insulin resistance in obese nondiabetic children. **Methods:** A PubMed database search was conducted, using 'metformin', 'obesity', 'insulin resistance', 'children', 'adolescents' as search terms. **Results:** Eleven trials were included in the present review. Metformin was administered for 6–12 months at a dosage of 1,000–2,000 mg/daily, decreasing BMI by 1.1–2.7 compared with placebo or lifestyle intervention alone. Concomitantly, fasting insulin resistance improved after metformin therapy. Posttreatment follow-up was performed in one study, showing that after 1 year of discontinuation of therapy the decrease in BMI disappears. **Conclusions:** Short-term metformin treatment appears to moderately affect weight reduction in severely obese children and adolescents, with a concomitant improvement in fasting insulin sensitivity. Further studies with

longer treatment period are needed to establish how much metformin can reduce weight and its real utility in preventing T2DM development in pediatric patients.

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Introduction

The past generation has witnessed a surge in the number of children, adolescents, and young adults with obesity and consequently a marked increase in the incidence of type 2 diabetes (T2DM) even in the youngest. Insulin resistance, strictly related to excessive weight gain, is the first step in the pathogenesis of T2DM, whose development requires pancreas β -cell function decline. It is clear from numerous investigations that intensive lifestyle intervention through diet and exercise (DE) can promote weight loss and insulin sensitivity and reduce the risk of developing T2DM [1, 2]. Thus, DE represent the foundation of care for all obese individuals and are critical components of any approach to therapy. Unfortunately, in the clinical practice the long-term success of lifestyle intervention alone is sometimes disappointing, and rates of obesity and T2DM in children and adults continue to increase [3]. This has stimulated the search for potential pharmacological approaches to prevent diabetes in chil-

Fig. 1. Mechanism of metformin action on hepatic and muscle glucose metabolism. AMPK = Adenosine monophosphate-activated protein kinase; ACC = acetyl-coenzyme A carboxylase; SREBP-1 = sterol regulatory element-binding protein-1.

dren and adolescents with obesity. Moreover, in severely obese adolescents with comorbidities present along with insufficient weight loss from a lifestyle modification program, bariatric surgery has become an acceptable treatment alternative provided that the bariatric surgery is performed in experienced tertiary institutions [4].

In the treatment of pediatric obesity, metformin has become a popular choice since its effectiveness, safety and multiple metabolic and cardiovascular benefits [5, 6].

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide currently used as an oral antihyperglycemic agent. It is currently the most widely used drug worldwide for the treatment of T2DM in adults. Its primary action appears to be the inhibition of hepatic glucose production and the increase in peripheral insulin sensitivity [7, 8] (fig. 1).

Metformin therapy in adolescents affected by T2DM is well established [8], although recent data from the TODAY study (Treatment Options for T2DM in Adolescents and Youth) [9] have showed discouraging results: 52% of adolescents with recent-onset T2DM treated with metformin alone manifested treatment failure within few years after diagnosis, implying that most youth with T2DM will require multiple oral agents or insulin therapy shortly after diagnosis.

Furthermore, metformin has also been demonstrated to be effective in restoring regular menses in girls with

polycystic ovarian syndrome [10], but not so valuable in ameliorating liver damage in children with non-alcoholic fatty liver disease [11]. Even if metformin is only approved in adolescents with T2DM older than 10 years and is not specifically indicated for the treatment of pediatric obesity, the adoption of treatment with metformin has been massively extended to obesity with normal glucose tolerance. Recent data show that unlicensed prescriptions of metformin in children and adolescents in UK had largely increased from 2000 to 2010 [12].

A series of randomized clinical trials have been carried out in obese children and adolescents to evaluate the potential impact of metformin on body weight and insulin resistance. In 2009, Park et al. [13] published a meta-analysis of five randomized controlled trials conducted in obese children without T2DM. They found that metformin was moderately efficacious, reducing BMI by 1.42 and homeostasis model assessment of insulin resistance (HOMA-IR) [14] score by 2.01. Since then, more trials have been published. However, the effectiveness of metformin in treating pediatric obesity with normal glucose tolerance remains controversial.

In this paper, a systematic analysis of the available literature is performed to assess the effect of metformin in reducing weight and counteracting insulin resistance in obese non-diabetic children and adolescents.

Materials and Methods

A literature search using the PubMed/MEDLINE database (last revision March 2013) was conducted. Search terms were 'metformin', 'obesity', 'insulin resistance', 'children', 'adolescents'.

Review articles, letters, commentaries, case reports or case series, studies on adults as well as studies on pediatric diabetes and other conditions different from pediatric obesity were excluded.

Fourteen trials were identified [15–28]. However, 3 studies [16, 20, 23] were excluded for their short duration (<6 months). Thus, 11 trials were selected for inclusion in this review. All the trials included are double-blind randomized placebo-controlled studies [15, 17–19, 22, 24, 25, 28], except 3 [21, 26, 27] which are not placebo controlled. In those studies, the metformin group (metformin plus lifestyle intervention) was compared with a lifestyle intervention alone group (placebo was not administered). In most of the trials, metformin was administered for 6 months; only in one study [24] was the treatment extended to 12 months.

The heterogeneity of the trials (different inclusion criteria, different or no lifestyle modification program, diverse type of indexes of insulin resistance/sensitivity, various dosage of metformin, different ethnicity) did not justify meta-analytic pooling of outcomes. Hence, we provide a best evidence synthesis.

Results

The characteristics of the studies included in the review are summarized in table 1.

Freemark and Bursey [15] in 2001 published the first trial on the use of metformin in pediatric obesity. They conducted a study in white and black high-risk adolescents. Participants received metformin (500 mg twice daily) or placebo. Metformin caused a modest, but statistically significant weight loss in children in the treatment group (BMI -0.5). In contrast, BMI rose slightly in placebo-treated patients ($+0.9$; $p < 0.02$). As a matter of fact, a placebo-subtracted reduction of 1.4 in BMI was observed in adolescents treated with metformin. Insulin sensitivity, assessed using the minimal model derived from rapidly sampled intravenous glucose tolerance test, did not change during the study. However, there was a small increase in insulin sensitivity as assessed by fasting indexes, including basal insulin, HOMA-IR and quantitative insulin sensitivity check index (QUICKI) [29].

Srinivasan et al. [17] conducted a crossover trial in children and adolescents of different ethnic background (mainly Asians and Caucasians). Patients were randomized to receive metformin (1,000 mg twice daily) and placebo for 6 months each in a crossover design, with a 2-week washout period between each treatment. Standardized information on healthy eating and exercise was

given, but a real lifestyle modification program was not undertaken. Each patient served as his/her own control. Metformin had a greater treatment effect on BMI compared with placebo (-1.26 ; $p = 0.002$). As in the previous study [15], metformin was effective in reducing fasting insulin, but not insulin sensitivity evaluated by the minimal model (derived from frequently sampled intravenous glucose tolerance test).

Atabek and Pirgon [18] conducted a trial in less obese adolescents from Turkey. Participants received metformin 500 mg twice daily (90 subjects) or placebo (30 subjects), plus individually tailored diet, exercise and behavioral therapy. Compared to placebo, metformin caused a substantial decrease in BMI (-2.1 ± 2.3 vs. 0.7 ± 2.5 ; $p = 0.001$) with a placebo-subtracted reduction of 2.7. Metformin was also more effective in reducing fasting insulin resistance and insulin area under the curve.

Love-Osborne et al. [19] performed a study on adolescents, mainly of Hispanic and African-American ethnicity. Participants were randomized to receive metformin at a maximum dose of 850 mg twice daily (70%) or placebo (30%), along with monthly goal setting for DE modification. At the end of the study, there was no overall difference in weight loss between subjects receiving metformin or placebo (BMI variation -0.16 ± 1.89 vs. 0.63 ± 1.29 ; $p = 0.11$). There were no statistical differences in the changes of fasting insulin between groups.

Clarson et al. [21] conducted a trial in obese Caucasian adolescents to assess the efficacy of adding metformin to lifestyle intervention in reducing BMI. Eleven participants received lifestyle intervention and metformin at a dose of 500 mg $\times$ 3 daily and 14 individuals lifestyle intervention alone. BMI significantly decreased by 1.8 with lifestyle and metformin treatment, but slightly rose with lifestyle intervention alone, with a 'lifestyle alone-subtracted reduction' of 2.3. HOMA-IR was significantly decreased in the lifestyle intervention group, but not following metformin and lifestyle intervention.

Wiegand et al. [22] performed a study in European adolescents, who had been previously treated with lifestyle intervention for 6 months with no success to evaluate if metformin was superior to lifestyle intervention alone in reducing obesity and insulin resistance. Participants were randomized into either the placebo ($n = 34$) or the metformin group (2×500 mg/day, $n = 36$) in addition to ongoing lifestyle intervention for another 6-month period in both groups. BMI remained unchanged in the metformin and in the placebo group. Fasting insulin and HOMA-IR decreased to an equal level in both groups, while whole body insulin sensitivity evalu-

Table 1. Metformin for treatment of obesity in children and adolescents with normal glucose tolerance: results from clinical trials

First author/ study group	Study type and duration, months	Inclusion/exclusion criteria	Age range, years	Mean BMI at baseline	Daily metformin dose, mg	Lifestyle intervention	Decrease in BMI compared to controls	Mean decrease in fasting insulin, μU/ml	Indices of insulin resistance/sensitivity variation
Freemark [15] (n = 29)	RCT 6	Fasting insulin >15 μU/ml At least 1 first- or second-degree relative with T2DM	12–19	41.5±0.9	500×2	None	-1.4	-12	QUICKI, HOMA-IR: improvement Minimal model: NS
Srinivasan [17] (n = 28)	RCT 6	Obesity defined according to International Obesity Task Force Insulin (mIU/l)/glucose (mmol/l) >4.5 and/or acanthosis nigricans Exclusion: preexisting diabetes	9–18	35.2±5.1	1,000×2	None	-1.3	-22	Minimal model: NS
Atabek [18] (n = 120)	RCT 6	BMI >95th percentile Exclusion: prior major illness including type 1 or type 2 diabetes	9–17	28.5±3.4	500×2	Individually tailored diet, exercise, behavioral therapy	-2.7	-14.6	QUICKI, HOMA-IR: improvement
Love-Osborne [19] (n = 85)	RCT 6	Fasting insulin >25 μU/ml or HOMA-IR >3.5 and 2 out of 3 factors (acanthosis nigricans, BMI >95th percentile, family history of T2DM) Exclusion: preexisting diabetes	12–19	39.4±6.5	850×2	Goal setting for lifestyle modification	NS	NS	NA
Clarson [21] (n = 25)	NPC 6	BMI >95th percentile HOMA-IR >3.0 Exclusion: fasting glucose >6.0 mmol/l	10–16	36.4±1.8	500×3	Structured lifestyle intervention program	-2.3	NS	HOMA-IR: NS
Wiegand [22] (n = 70)	RCT 6	No success after 6 months-lifestyle intervention defined as ΔBMI <2, HOMA-IR >3 or >95th percentile	12–18	33.1±4.6	500×2	Multiprofessional struc- tured lifestyle interven- tion program	NS	-4.5 (NS vs. placebo)	HOMA-IR: improvement (NS vs. placebo) ISI: improvement
Glaser pediatric research network [24] (n = 77)	RCT 12	BMI >95th percentile Exclusion: preexisting diabetes	13–18	35.9±5.7	2,000 XR	Structured lifestyle intervention program	-1.1	NA	HOMA-IR, ISI: NS
Yanovski [25] (n = 100)	RCT 6	BMI >95th percentile Prepubertal or early pubertal Fasting insulin ≥15 μU/ml Exclusion: impaired fasting glucose, diabetes	6–12	34.2±6.8	1,000×2	Not intensive lifestyle intervention program	-1.1	-3.24	HOMA-IR: improvement Insulin sensitivity (hyperglycemic clamp): NS
Rynders [26] (n = 16)	NPC 6	BMI >95th percentile Late puberty Exclusion criteria: elevation of blood pressure, fasting glucose, cholesterol, triglycerides	10–17	33.6±7.2	500×2 (<12 years) 1,000×2 (≥12 years)	Structured lifestyle intervention program	-1.7	NA	NA
Mauras [27] (n = 42)	NPC 6	As for Rynders [23] plus C-reactive protein and/or fibrinogen >2 SD	8–17	32.0±1.0	500×2 (<12 years) 1,000×2 (≥12 years)	Structured lifestyle intervention program	-1.3	NS	HOMA-IR: NS

Table 1. (continued)

First author/ study group	Study type and duration, months	Inclusion/exclusion criteria	Age range, years	Mean BMI at baseline	Daily metformin dose, mg	Lifestyle intervention	Decrease in BMI compared to controls	Mean decrease in fasting insulin, μU/ml	Indices of insulin resistance/sensitivity variation
MOCA trial [28] (n = 151)	RCT 6	BMI >98th percentile Impaired glucose tolerance or fasting insulin >26 μU/ml or 120-min insulin >89 μU/ml (pubertal/postpubertal children); fasting insulin >15 μU/ml or 120-min insulin >89 μU/ml (prepubertal children) Exclusion: glycosuria, ketonuria, chronic illness, chromosomal abnormality, syndrome, previous episode of lactic acidosis	8–18	36.5±6.3	1,000+500	Not intensive lifestyle intervention program	-1.07	NS	HOMA-IR, QUICKI, ISI: NS

RCT = Randomized placebo-controlled study; NPC = not placebo controlled study; NS = not significant; NA = not available.

ated by the Matsuda index (insulin sensitivity index, ISI) [30] only decreased in the metformin group.

The Glaser Pediatric Research Network [24] performed a multicenter study to evaluate if the extended release (XR) formulation of metformin was effective in reducing BMI in obese adolescents. Seventy-seven multi-ethnic obese adolescents were randomized to receive metformin XR 2,000 mg once daily, or an identical placebo, in addition to lifestyle intervention program in both groups. Furthermore, participants were monitored for an additional 12-month period after discontinuation of pharmacological therapy.

Metformin XR caused a modest, but significant reduction of adjusted BMI (-0.9). In contrast, BMI rose slightly in placebo-treated patients (+0.2; $p = 0.03$). As a matter of fact, a placebo-subtracted reduction of 1.1 in BMI was observed in adolescents treated with metformin XR. No significant effects of metformin XR on insulin indices (HOMA-IR, ISI, insulin area under the curve) were observed. Moreover, the positive effect of Metformin XR on BMI waned at the end of the posttreatment 12-month period.

Yanovski et al. [25] conducted a trial consisting of multiethnic younger children. Participants were randomized to receive metformin 1,000 mg twice daily ($n = 53$) or placebo ($n = 47$). In addition, all children and their parents participated in a monthly dietitian-administered weight reduction program. The randomized trial was followed by an open-label metformin treatment for further 6 months. Children prescribed metformin had a significantly greater decrease in BMI (with a placebo subtracted difference of -1.09). Fasting serum insulin and HOMA-IR also improved more in the metformin-treated children than in those treated with placebo. However, insulin sensitivity estimated from the hyperglycemic clamp study did not differ between the two groups.

During the 6-month open-label phase, subjects who previously received placebo significantly decreased BMI z score; subjects treated continuously with metformin had nonsignificant increases in BMI z score compared with their 6-month values and increases in absolute BMI consistent with those expected to occur as children mature.

Rynders et al. [26] performed a study in adolescents to evaluate if changes in cardiorespiratory fitness, after structured DE or DE plus metformin were effective in modifying adiposity and metabolic risk factors. Participants were randomized into a structured lifestyle program consisting of DE ($n = 9$) or DE plus metformin ($n = 7$; 500 mg $\times$ 2 daily in subjects <12 years, 1,000 mg $\times$ 2 daily in subjects $\geq$ 12 years). DE plus metformin was

more efficacious than DE alone in reducing BMI, with a 'DE alone group-subtracted reduction' of 1.7. However, metformin did not provide benefits above lifestyle modification alone for improving cardiorespiratory fitness.

Mauras et al. [27] published a paper that is a part of a larger study (including the trial of Rynders et al. [26]) aimed at evaluating the effects of metformin plus lifestyle. As in the previous study [26], participants were randomized into a structured lifestyle program consisting of DE (n = 19) or DE plus metformin (n = 23). BMI loss was more pronounced in DE plus metformin (-2.4 ± 0.5) than in DE group (-1.1 ± 0.5), with a DE alone group-subtracted reduction of 1.3. Surprisingly, fasting insulin concentration and HOMA-IR increased in both groups, but fasting insulin increased less in the metformin group.

The recently published MOCA trial (metformin in obese children and adolescents) [28], is a multicenter trial conducted in six pediatric centers in the UK, aimed at evaluating the effect of metformin on BMI-SDS. Most of participants were white British, but 24% were of ethnic minorities (British Asian or Afro-Caribbean). Children and adolescents were randomized to receive metformin (1,000 mg in the morning, 500 mg in the evening), or an identical placebo. All participants were provided with standardized healthy lifestyle advice. Metformin was associated with a significant reduction in BMI compared with placebo (mean adjusted difference between groups -1.07 , $p = 0.005$). No significant effects of metformin on insulin resistance indices (fasting insulin, HOMA-IR, ISI) were observed.

Discussion

Eleven studies of the effect of metformin on managing pediatric obesity have been reviewed in this paper (table 1). Most of them [15, 17–19, 21, 22, 24, 26–28] were primarily focused on adolescents; only the trial of Yanovski et al. [25] examined mostly younger children.

Nine [15, 17, 18, 21, 24–27] out of 11 studies found a small, but significant benefit of metformin in reducing weight after 6–12 months of treatment. Metformin decreased BMI from 1.1 up to 2.7 compared with placebo or lifestyle intervention alone.

Fasting insulin and fasting indexes of insulin resistance (HOMA-IR and QUICKI) were reduced in many studies [15, 17, 18, 22, 25], but not all [19, 21, 27, 28]. Nevertheless, insulin sensitivity evaluated by the minimal model derived from either frequently sampled intrave-

nous glucose tolerance test or hyperglycemic clamp did not change [15, 17, 25].

Taking together, these results suggest a very modest effect for metformin as an anti-obesity drug. Except for the study of Atabek and Pirgon [18] who found a good decrease in BMI (-2.7) following metformin treatment plus lifestyle modification program in moderately obese adolescents (mean BMI 28), the trials showed a very modest weight decrease in children and adolescents with severe obesity (mean BMI >32). In the latter case, a reduction of 1.1–1.7 after 6–12 months appears to be a vain result.

Additionally, results from the Glaser Pediatric Network [24] showed that after 1 year of discontinuation of therapy, the small decrease in BMI obtained with metformin XR, disappears.

Different indexes of insulin resistance/sensitivity were considered in the various trials, making difficult to derive a clear conclusion on the effect of metformin on insulin metabolism. As might be anticipated, because of its major effect to suppress hepatic gluconeogenesis [31], many of the studies showed that metformin only improved fasting insulin [15, 17, 18, 25], HOMA-IR and QUICKI [15, 18, 25], measures of insulin sensitivity that appear principally to reflect hepatic sensitivity to insulin's action [32], but that metformin did not greatly alter whole-body (primarily muscle) insulin sensitivity [15, 17, 25]. Nevertheless, in the trial on obese European adolescents [22], metformin was efficacious in reducing whole-body insulin sensitivity evaluated by the Matsuda index (ISI) [30], without decreasing BMI, making difficult to interpret these apparently contrasting results.

It must be noted that the trials were relatively short term: subjects were treated with metformin for a period no longer than 6 months. Only in the study of the Glaser Pediatric Network [24] was the metformin treatment extended to 12 months. Moreover, some of the studies [15, 17, 18, 21, 26, 27] were based on small samples. Unfortunately, longer-term data of a wider sample on the effectiveness of metformin in reducing weight and preventing T2DM development in obese children and adolescents are not available.

Various dosage of metformin was used in the different trials ranging from 1,000 to 2,000 mg per day. Apparently, there was no correlation between the dose of metformin and the degree of BMI decrease. Indeed, the best result in terms of BMI was obtained with the lowest dose (1,000 mg daily) in the study of Atabek and Pirgon [18] on less severe obese adolescents. This could suggest that the less severe obesity at the beginning of the study or the

lifestyle program undertaken could have had a major role rather than the dose of metformin.

Most trials were conducted in Caucasian patients, but some studies [15, 18, 19, 27, 28] included ethnic minorities, and this could explain some of the variability in the response to metformin treatment in terms of changes in insulin sensitivity.

Different lifestyle programs were undertaken in the various studies, ranging from no intervention [15, 17], to intensive multidisciplinary [22, 24, 26, 27] lifestyle program with weekly dietary counseling, free memberships to use facilities to exercise [26, 27], or individually tailored DE [18, 21]. Thus, the lifestyle interventions, crucially implicated in the outcomes of the present review (weight loss and insulin sensitivity improvement in obese children), were extremely inhomogeneous. This was the main reason for not doing a meta-analytic pooling of data coming from so different treatment approaches and for performing a descriptive summary of the available literature. Nevertheless, the studies on severely obese children and adolescents with the largest sample size [25,

28] and the longest follow-up period [24] come to the same conclusion: metformin minimally influences weight loss. However, we are aware that our methodological approach (a description of the literature and not a meta-analysis) is the major limit of our study as weight cannot be given to the studies depending on, for example, sample size and other factors, and confidence intervals cannot be provided.

In conclusion, metformin treatment appears to minimally affect weight reduction in severely obese children and adolescents. Indeed, a reduction of 1.1–1.7 of BMI in a severely obese adolescent is likely clinically irrelevant in terms of true improvement in cardiovascular risk.

Further studies with larger sample size and longer treatment period are needed to establish how much metformin can reduce weight and the most appropriate dose in pediatric patients. Additionally, the real utility of metformin in children and adolescents to delay/prevent the development of T2DM, as for adults, needs to be confirmed: data from adults have showed that metformin can delay the incidence of T2DM [2, 33].

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