Metformin for obesity in children and adolescents: a systematic review

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**Objective:** To summarize the efficacy of metformin in reducing body mass index (BMI kg/m$^2$) and cardiometabolic risk in obese children and adolescents without diabetes.

**Research Design and Methods:** Systematic review and meta-analysis of randomized controlled trials (RCTs). Double-blind RCTs of duration $\geq 6$ months in obese subjects aged $\leq 19$ years without diabetes were included. Primary outcomes of interest: changes in BMI and measures of insulin sensitivity.

**Results:** Five trials met inclusion criteria (n=320 individuals). Compared to placebo, metformin reduced BMI by 1.42 kg/m$^2$ (95% CI 0.83 to 2.02 kg/m$^2$) and homeostasis model assessment insulin resistance (HOMA-IR) score by 2.01 (95% CI 0.75 to 3.26)

**Conclusion:** Metformin appears to be moderately efficacious in reducing BMI and insulin resistance in hyperinsulinemic obese children and adolescents in the short term. Larger, longer-term studies in different populations are needed to establish its role in the treatment of overweight children.
Metformin has been shown to reduce weight gain, hyperinsulinemia and hyperglycemia in adults with type 2 diabetes (1; 2), and to reduce progression from impaired glucose tolerance to diabetes in those without diabetes (3). These benefits have led to an increase in the use of metformin in obese children with hyperinsulinemia. However, obesity is not a licensed indication for metformin in the UK or the US, and use has proceeded faster than evidence for benefit. We undertook a systematic review of randomized controlled trials (RCTs) investigating the efficacy of metformin for reducing body mass index (BMI) and cardiometabolic risk in obese children without diabetes.

RESEARCH DESIGN AND METHODS

We searched Ovid MEDLINE, EMBASE, the Cochrane Register of Controlled Trials, the metaRegister of Controlled Trials, and key journals published before December 2008. We included double-blind RCTs of duration ≥6 months in obese subjects aged ≤19 years without diabetes and without secondary or syndromic causes of obesity. Primary outcomes of interest were BMI (kg/m²) and measures of insulin sensitivity. Secondary outcomes included fat mass, blood pressure, fasting lipids, and adverse effects.

Where ≥3 studies reported a common outcome, treatment effect was explored in a meta-analysis (Stata Statistical Software 10.1, StataCorp 2007), pooling data from the end of the follow-up period for trial completers. A random-effects model was selected. Sensitivity analyses were performed using fixed effects models, and by dose of metformin (1000mg versus 2000mg), age of participants (12-19 years versus <12 years), co-intervention (metformin versus metformin+co-intervention), baseline BMI (mean ≥35 kg/m² versus <35 kg/m²), and by excluding one study reporting greater treatment effects than the other studies (4).

RESULTS

Five studies published between 2001 and 2008 met the inclusion criteria, including one crossover trial (5).

Three studies took place in the USA (6-8), and one each in Australia (5), and Turkey (4). All trials lasted 6 months, with metformin doses from 1000 to 2000 mg per day. Three studies used lifestyle co-interventions in both trial arms (4; 7; 8). Two studies included adolescents (aged 12-19 years) (6; 7), one looked at younger children (6-12 years) (6), and the others spanned ages 9-18 years. In the American and Australian studies, a large proportion of participants (45-90%) were from ethnic backgrounds with high prevalence of metabolic syndrome (African-American, Hispanic or Asian). All participants were hyperinsulinemic or insulin resistant. Sample size ranged from 28 to 120 participants at randomization; in total there were 365 participants and 320 trial completers. Mean attrition rates were 11% in metformin groups and 16% in placebo groups.

In the pooled analysis, metformin reduced BMI by a mean of 1.42 kg/m² (95% CI 0.83 to 2.02 kg/m²) compared with placebo (I²=56.2%; n=342) (Figure 1). Sensitivity analyses did not reveal notable differences by age, dose, or baseline BMI. When the outlier result was excluded, metformin reduced BMI by 1.15 kg/m² (0.73 to 1.57, I²=0%) Reduction in fasting insulin was greater in metformin than placebo groups in three studies, but evidence for a treatment effect was weak (-5.30 µU/mL, 95% CI -11.96 to +1.36 µU/mL, I²=78.7%; n=257) (4-7). Pooled metformin effect on HOMA-IR score was -2.01 (-3.26 to -0.75, I²=49.5%; n=234) (4; 6; 8) and -1.28 (-2.55 to -0.21, I²=0%) if the Turkish study was excluded.

Pooled mean metformin effect on total cholesterol was -0.19 mmol/L (-0.38 to -0.01,
Analyses did not provide strong evidence for a treatment effect on fasting glucose, HDL-cholesterol, triglyceride levels, or blood pressure. There was insufficient data to comment on body fat outcomes. Gastrointestinal (GI) problems were the most commonly reported side effect (in 20-30%) and were more frequently reported in metformin than in placebo groups (risk difference 10-14% (6; 7)). Only one participant reported GI problems as the reason for leaving a study (7).

**CONCLUSIONS**

Our meta-analysis provides some support for a beneficial metformin effect on obesity outcomes among hyperinsulinemic children and adolescents. Treatment over 6 months may be efficacious in reducing BMI by 1.42 kg/m\(^2\) (equivalent to 0.4 standard deviation (SD), based on SD for BMI in UK and US adolescents), and HOMA-IR score by 2.01 (~0.63 SD (9)). Metformin use was also associated with a small reduction in total cholesterol level (~0.26 SD (10)), but these are unadjusted measures and it is not possible to determine whether effects are secondary to reductions in BMI and HOMA-IR, or attributable to other factors. To our knowledge, the effects of metformin on BMI in obese children without diabetes have been synthesised in only one published review based on three studies (11), which identified no treatment effect at 6 months (-0.17 kg/m\(^2\), 95% CI -0.62 to 0.28).

Metformin may not be as effective as behavioural interventions in reducing BMI: a meta-analysis of behavioural interventions in obese adolescents reported an effect of -3.04 kg/m\(^2\) (-3.14 to -2.94) at 6 months, which was maintained at 12 months follow-up (12). When compared to drugs that are licensed for obesity, metformin has moderate effect: meta-analyses of RCTs reported an orlistat effect of -0.76 kg/m\(^2\) (-1.07 to -0.44), and a sibutramine effect of -1.66 kg/m\(^2\) (-1.89 to -1.43) at 6 months (12).

The results of this review must be interpreted with caution: studies were short-term and based on small samples; participants were mainly from the USA and a large proportion were from ethnic backgrounds known to be at increased risk of metabolic disorders, limiting the generalisability of findings; and studies presented unadjusted measures and without intention-to-treat analyses, which may have overestimated treatment effects.

Metformin may be efficacious in reducing BMI and insulin resistance among obese hyperinsulinemic children and adolescents in the short term. Larger, long-term studies across different populations are needed to establish the role of metformin as therapy for obesity and cardiometabolic risk in young people.

**ACKNOWLEDGEMENTS**

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**Contribution to authorship:** MHP contributed to the protocol, search strategy, literature searches, study selection, data extraction, data synthesis and manuscript writing. RV and SK conceived the review and contributed to the protocol, study selection and manuscript writing. KJW contributed to the protocol, search strategy, data extraction and data synthesis. BW contributed to data extraction. All authors commented on the manuscript.

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REFERENCES
Figure 1: Forest plot comparing change in BMI (kg/m²) in metformin and placebo groups
Figure 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Weight</th>
<th>WMD (95% CI)</th>
</tr>
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<tr>
<td>Atabek</td>
<td>17.52</td>
<td>-2.73 (-3.74, -1.72)</td>
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<tr>
<td>Freemark</td>
<td>22.39</td>
<td>-1.40 (-2.17, -0.63)</td>
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<tr>
<td>Love–Osborne</td>
<td>21.13</td>
<td>-0.79 (-1.62, 0.04)</td>
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<tr>
<td>Srinivasan</td>
<td>17.91</td>
<td>-1.26 (-2.25, -0.27)</td>
</tr>
<tr>
<td>Yanovski</td>
<td>21.05</td>
<td>-1.14 (-1.97, -0.31)</td>
</tr>
<tr>
<td>Overall</td>
<td>100.00</td>
<td>-1.42 (-2.02, -0.83)</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

*Favors Metformin *Favors placebo