Review

Metformin Therapy in Obese Insulin-Resistant Adolescents: A 6-Month Trial

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Abstract

Background

Childhood obesity has increased significantly in recent decades and is currently considered a public health problem. Obesity affects children and adolescents, increasing insulin resistance and risk for type 2 diabetes. Current treatments have low effectiveness in weight loss.

1.2 Objective

To determine whether metformin treatment for 6 months is effective in reducing body weight and hyperinsulinemia in obese adolescents.

Methods

Retrospective, descriptive study of obese insulin-resistant adolescents, without other metabolic comorbidities, undergoing therapy with metformin over a period of 6 months. Data were collected from clinical records at CHVN Gaia/Espinho.

Results

Nineteen adolescents (age range 13-17), 53% females, with mean body mass index (BMI) at first evaluation of 30.14 kg/m^2 were included in this study. Average HOMA-IR (homeostasis model assessment for insulin-resistance index) was 5.7 (minimum 3.5, maximum 9.9). All patients began treatment with metformin in doses that ranged from 500 to 2000 mg/day for a period of 6 months. There were no significant side effects or therapeutic discontinuation. After metformin, there was a decline in BMI (- 0, 71 Kg/m^2) and HOMA-IR (- 1, 1), in 68, 42% and 75% adolescents, respectively. Greater changes were seen in groups with higher doses of metformin. In most cases, the decrease in BMI and HOMA-IR variation with different metformin doses.

Conclusion

These data suggest that metformin treatment improves markers of insulin sensitivity and reduces BMI in obese insulin-resistant adolescents. Stronger evidence from high-quality studies of longer duration and larger sample size are required, before clinical conclusions about the optimal treatment protocol in this population can be drawn.

Introduction

Childhood obesity has become the most common pediatric disorder in the developed world. Its prevalence has increased dramatically in the last decade becoming today an epidemic of global proportions [1].

Obesity at a young age puts individuals at a greater risk for serious health problems, including hypertension, diabetes, high cholesterol and cardiovascular disease (CVD) [2].

Among 5 to 17-year-old children in a population-based sample, 70% of subjects had at least one CVD risk factor, while 39% of subjects had two or more CVD risk factors [3].

Regarding type 2 diabetes mellitus (DM2), in most cases starts with overweight, insulin resistance and dyslipidemia, advancing through a phase of fasting or postprandial hyperglycemia (glucose intolerance) before the onset of symptoms [4].

Insulin resistance (IR) is a state in which a given concentration of insulin is associated with a subnormal glucose response. Important long term consequences include the development of type 2 diabetes, cardiovascular disease and certain malignancies [5].

High serum free fatty acid concentrations in the circulation, either derived from enlarge adipose cells (the storage capacity of which has been exceeded) or because there is not enough storage space in the adipose tissue of lipodystrophic subjects, have been implicated in the pathogenesis of obesity-related metabolic disorders [1].

Increased release of adipocytokines, such as tumor necrosis factor (TNF-alpha) or decreased production of protective adipocytokines, such as adiponectin, are thought to mediate the effects of obesity in the pathogenesis of insulin resistance, and subsequently, the metabolic syndrome and type 2 diabetes [5,6].

Treatment of pediatric obesity is imperative to the overall health and wellness of children and adolescents. Support for lifestyle

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modification (dietary and behavioral modification and physical activity) for both children and their families is essential for healthy living and a prerequisite for all overweight and obesity treatments [8].

The outcome of lifestyle interventions remains insufficient and the adjuvant role of pharmacological agents has been proposed. Among the group of weight-loss medications, orlistat is the only pharmaceutical approved by the US FDA for the treatment of overweight and obese adolescents [1].

Metformin is a biguanide derivative used for the treatment of type 2 diabetes mellitus in adults and children at least 10 years of age. It activates adenosine monophosphate-activated protein kinase to reduce hepatic glucose production, decrease intestinal glucose absorption, and increase insulin sensitivity by way of improved peripheral glucose uptake and utilization [9]. Additionally, metformin inhibits fat cell lipogenesis and may reduce food intake by increasing a glucogen-like peptide [10].

Although metformin is not FDA-approved for treating pediatric obesity, it has been evaluated in several small clinical trials and its off-label use may be effective in improving weight loss and reducing insulin resistance [8, 10].

This study aimed to determine whether metformin treatment for 6 months is effective in reducing body weight and hyperinsulinemia in obese adolescents.

Methods

The present study used data collected from clinical records of adolescents followed in pediatric endocrinology consultations at CHVN Gaia/Espinho. It is therefore a retrospective, descriptive study of obese insulin-resistant adolescents, without other metabolic comorbidities, undergoing therapy with metformin over a period of 6 months. Patients with body mass index (BMI) > 97th percentile for age and sex and homeostasis model assessment for insulin-resistance index (HOMA-IR) > 3,43, were included in this study.

In basal physiological conditions (after overnight fasting), blood levels of insulin and glucose can be correlated, which allows calculation of a sensitivity (or resistance) index to insulin, like HOMA-IR. Although dynamic studies, like euglycemic insulin clamp technique, have been considered to be the gold standard of insulin resistance assessment, these techniques are impractical for routine clinical use. Thus, HOMA-IR has a good correlation with the most reliable techniques, it's easy to determine and is reproducible [5,12].

Since there are no consensual cut-off levels for HOMA-IR in adolescents, we used a value stated from a cross-sectional study in a Spanish pediatric population [13].

Results

We studied nineteen adolescents, mean age 14, 1 (age range 13-17), 53% females (n= 10).

At first appointment, mean BMI was 30.14 kg/m². This value was slightly higher in girls (30, 44 kg/m² vs. 29,8kg/m² in boys). Average HOMA-IR was 5.7 (minimum 3.5, maximum 9.9). 80% of patients showed acanthosis nigricans and 65% striae. One patient had hirsutism. No subject had dyslipidemia or liver enzyme abnormalities.

All patients began treatment with metformin in doses that ranged from 500 to 2000 mg/day, for a period of 6 months. Nearly half of the patients received doses of 1000 mg/day (Table 1).

There were no significant side effects, including hypoglycemia, or therapeutic discontinuation.
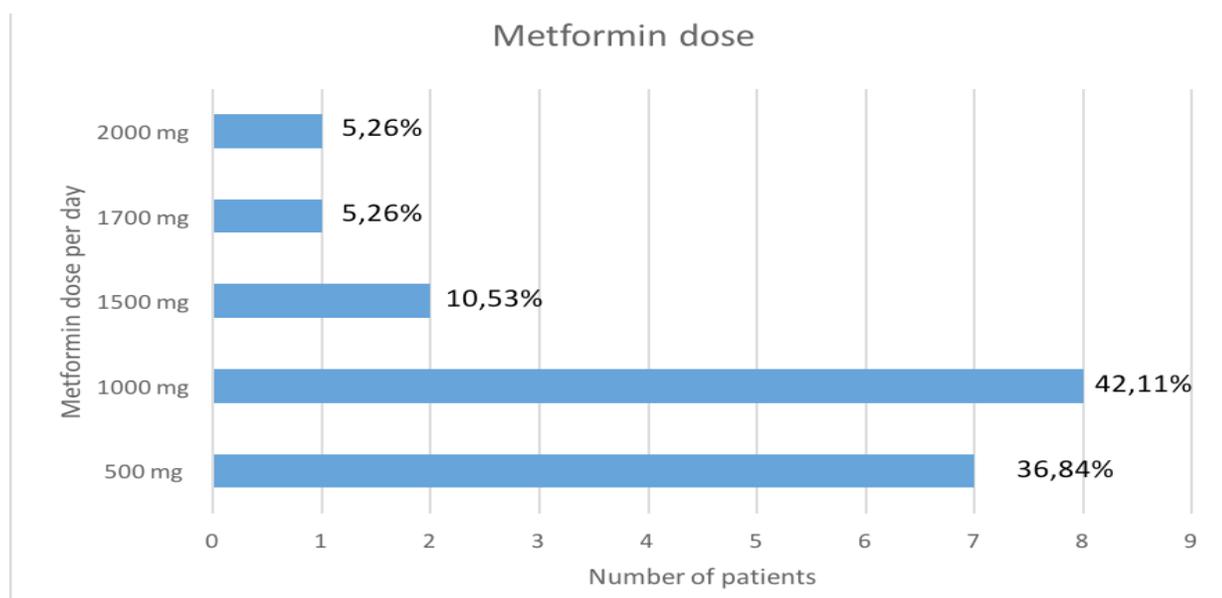

Table 1: Metformin dose

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After metformin, there was a decrease in BMI in 68, 42% patients, with a mean decrease of 0, 71 kg/m² (from 30.14 to 29, 43 kg/m²) (Table 2). This reduction was more pronounced in boys (- 1 kg/m²) than in girls (- 0.37 Kg/m²).
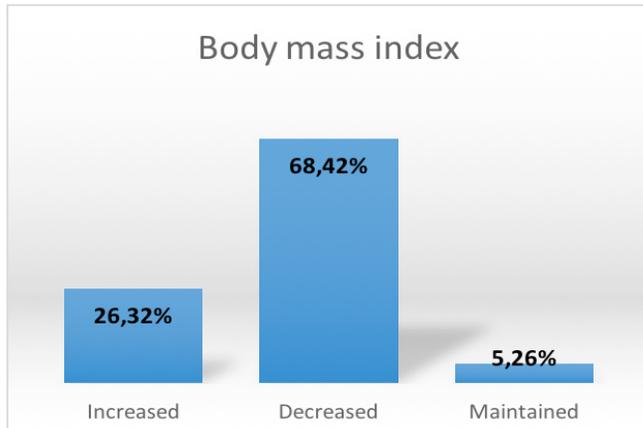
Table 2: Body mass index after 6 months of metformin therapy

In analytic reassessment, at 6 months, HOMA-IR declined in 75% of cases, and his final average was 4.6 (- 1.1)

Greater changes were seen in groups that received higher doses of metformin (Table 3).

In most cases, there was a simultaneous decrease in BMI and HOMA-IR. Indeed 85% of patients with reduction in BMI had also shown a decrease in HOMA-IR.

Discussion

After 6 months of metformin, there was clinical and analytical improvement, with decrease of BMI and HOMA-IR. However, the study period was relatively short and the study sample was small.

Even though these positive results, a high percentage of adolescents abandon treatment after 6 months of therapy. For that reason, it's very difficult to assess therapeutic efficacy of metformin in longer periods of treatment.

As previously reported, groups receiving higher doses of metformin achieved better results. Differences between metformin doses used in this study are explained by the fact that each physician has its own therapeutic criteria. Since there are no guidelines on when to start treatment with metformin or what dose to use, this variability is understandable. Nevertheless, we found that higher doses are associated with better outcomes, without more collateral effects.

In most patients, decrease in BMI was complemented by decrease in HOMA-IR. However, 15% of adolescents who lost weight did not improve their insulin sensitivity index. In this group lower doses of metformin were used. So, it appears that metformin effects on weight loss and glucose metabolism are dose-related, with higher doses required for treatment of insulin resistance.

We cannot fail to mention the importance of lifestyle interventions in the achievement of these results. Actually, the promotion of these interventions is held on the first medical evaluation of all patients. However, it is naturally difficult to assess their individual contribution.

Conclusion

In accordance with findings published in the medical literature, metformin appears to have a significant effect on weight loss. However, in this study, contrary to that seen in these works, there was efficacy of metformin in reducing insulin resistance.

Table 3: BMI and HOMA-IR variation with different metformin doses

Metformin dose (mg/day)	BMI before metformin	BMI after metformin	HOMA before metformin	HOMA after metformin
500	28,5	32,2	4,5	6,8
500	29,2	30,5	3,8	4,9
500	32,5	36	3,7	5,2
500	28,6	26,5	3,5	2,5
500	30	30	6,5	6,2
500	40,9	40,8	5,5	6
500	26	21	4,2	3,5
1000	30	32	5,3	5
1000	30,24	29,17	3,56	1,44
1000	26,99	25,9	9,9	12,3
1000	35,9	33	9,2	4,6
1000	27,45	25,6	8	2,2
1000	31,2	26	4,2	2,45
1000	27,5	27,29	6,74	5,18
1000	26	24	6,6	5,1
1500	31,6	30,2	7,3	6,7
1500	26	23	4,1	1,1
1700	32,5	34,9	4,5	2,2
2000	31,7	31,2	7,3	4,1

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Further studies are needed, with larger number of participants and longer follow-up, to identify potential candidates for therapy with metformin.

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