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USE OF METFORMIN IN PEDIATRIC TYPE 2 DIABETES

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Abstract

In the last 10 years the incidence of type 2 diabetes (T2DM) in children and adolescents has increased, due to increasing prevalence of obesity in youth. Therefore, the prevalence of diabetes-related complications such as hypertension, hyperlipidemia and microalbuminuria has also increased in pediatric T2DM. The pathogenesis of T2DM in children involves genetic and environmental factors that will determine the increase of insulin resistance and decrease of beta pancreatic insulin secretion. Only metformin and insulin are approved for clinical use in children in the majority of countries. The aim of this paper is to review the benefits of the treatment with metformin in children and adolescents with T2DM.

key words: *type 2 diabetes mellitus, children/adolescents, metformin.*

Introduction

The real prevalence of pediatric type 2 diabetes (T2DM) is unknown in many countries. However, it seems that the incidence of T2DM in children is increasing, so the American Diabetes Association (ADA) recommends screening of at-risk asymptomatic children [1]. T2DM in children and adolescents is more common in some minority populations: black African descents, Central and South Americans, native North Americans, South Asians (Indian Peninsula), Asians and Native Pacific Islander [2]. In the United States, T2DM represented about 3% of pediatric diabetes in 1990. Approximately ten years later, in 2003, it represented 20% of pediatric diabetes [3,4].

Obesity, positive family history for diabetes, belonging to specific racial and ethnic groups, female gender and conditions associated with insulin resistance such as polycystic ovary syndrome (PCOS), are the risk factors increasing the risk for childhood onset T2DM. At the onset of puberty (generally around the mean age of 13.5 years [4,5] when insulin resistance is increased by approximately 30% due to the increased secretion of growth hormone and insulin-like growth factor-1), children at risk can develop T2DM [6,7].

The risk factors for cardiovascular disease may already exist at the time of diagnosis and recent studies have shown that the rates of hypertension, dyslipidemia and microalbuminuria in adolescents with T2DM are significantly higher than in adolescents with T1DM [8,9].

In January 2013, the American Academy of Pediatrics (AAP) published the guideline for the

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management of newly diagnosed T2DM in children and adolescents that provides evidence-based recommendations for pediatric T2DM. This new clinical guideline is addressed to the primary care physicians on managing T2DM in children and adolescents aged 10-18 years [10].

Screening for T2DM in asymptomatic children

ADA recommends screening for T2DM in asymptomatic children who are overweight or obese and who have two or more additional risk factors for diabetes [1]. According to ADA guidelines, the following criteria are used to identify the children at risk:

- *"Overweight (BMI ≥85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)*
- *Plus any two of the following risk factors:*
- *Family history of T2DM in first- or second-degree relative*
- *Race/ethnicity*
- *Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational age birth weight)*
- *Maternal history of diabetes or gestational diabetes mellitus during the child's gestation"*

ADA recommends beginning screening at the age of 10 years or at onset of puberty (if puberty occurs at a younger age) and repeating the screening every 3 years [1].

Recommendations for management of T2DM in children and adolescents

Weight loss, increase in exercise capacity, normalization of glycemia and control of comorbidities (hypertension, dyslipidemia, hepatic steatosis and nephropathy) are important components in the management of pediatric T2DM [2].

Lifestyle changes in diet and exercise are recommended to increase insulin sensitivity in addition to pharmacologic therapy [2]. Currently, metformin is the only Food and Drug Administration (FDA) approved oral treatment for T2DM in children and youth while insulin is approved in many countries [11]. Sulphonylureas are approved for pediatric use in some countries [1].

Metformin is the most used oral anti-hypergylcemic agent in T2DM, inhibiting hepatic glucose production, increasing peripheral and liver sensitivity to insulin and decreasing intestinal glucose uptake [12]. An excellent review of the molecular mechanisms of metformin action on hepatic gluconeogenesis was recently published [13].

Metformin has also anti-lipolytic effects, lowering circulating free fatty acid levels. *In vivo* and *in vitro*, metformin activates the adenosine monophosphate-activated protein kinase pathway (AMPK), increasing fatty acid oxidation in hepatocytes, skeletal muscle cells and mouse ovarian tissue and decreasing glucose production [14]. In girls with polycystic ovary syndrome (PCOS), metformin may normalise ovulatory abnormalities increasing pregnancy risk. The contraindications for metformin are hepatic diseases, renal impairment, cardiac or respiratory insufficiency, alcohol abuse. It should be discontinued before performing radiographic tests with contrast agents and during gastrointestinal illness [2].

Regarding the effect on glycated hemoglobin (HbA1c), "*metformin has the advantage over sulphonylureas of similar reduction in glycated hemoglobin (HbA1c) without the risk of hypoglycaemia and long-term use is associated with a 1-2% reduction in HbA1c*" [2].

The global International Diabetes Federation (IDF) and International Society for Pediatric and Adolescent Diabetes (ISPAD) Guideline

recommend metformin as the initial pharmacologic treatment in pediatric subjects with T2DM. The same guideline recommends to "*begin with 250 mg daily for 3-4 days, if tolerated, increase to 250 mg twice a day, titrate over 3-4 weeks until the maximal dose of 1000 mg twice a day*" [2].

Efficacy and safety of treatment with metformin in pediatric subjects

A study performed by Gottschalk M *et al.* compared the efficacy and safety of the treatment with glimepiride *versus* metformin in children and adolescents with T2DM inadequately controlled with lifestyle intervention alone or with oral monotherapy [15]. In this study, 285 children aged 8-17 years old with HbA1c between 7.1% and 12% were randomized to receive glimepiride 1mg-8mg once daily or metformin 500mg-1000 mg twice daily for 24 weeks. All the children were included in two age-related groups (≤12 years or >12 years) and randomly assigned in a one-for-one ratio to receive glimepiride or metformin for 24-weeks. The study showed a significant reduction from baseline in HbA1c for both the glimepiride (-0.54%, p=0.001) and metformin (-0.71%, p=0.0002) groups. So, glimepiride reduced HbA1c similarly to metformin but with greater weight gain (1.97 kg in the glimepiride group and 0.55 kg in the metformin group, p=0.005) while the percent of children who had one or more adverse events was similar between the two groups: (59.2% glimepiride and 57.7% metformin) [15].

In a randomized controlled trial published in 2002 in Diabetes Care, *Jones KL et al*. reported that metformin significantly lowered HbA1c after 16 weeks compared with placebo (7.5% versus 8.6%) for the maximum tolerated dose of 2000 mg/dl, in adolescents with new-onset T2DM [16].

Flint A *et al.* reported that the majority of T2DM children and adolescents maintain good glycemic control (HbA1C<7%) with metformin and lifesyle intervention for the first 2-3 years of disease [17].

In another study [18], Gómez-Díaz RA *et al.* studied the effect of metformin on resistin and other markers of insulin resistance and inflammation in children with glucose intolerance aged 4 to 17 years. A total of 52 patients (11.9±2.6 years old) were randomized to receive 850 mg metformin or placebo twice daily for 12 weeks, period during which they received an iso-caloric diet and followed an exercise program. 28 patients (12males/16 females) received metformin and 24 placebo (11males/13 females). The study showed that metformin was associated with a significant decrease in Homeostasis Model of Assessment - Insulin Resistance (HOMA-IR) index (p=0.032) and HbA1c levels (p=0.001). The percent of patients with weight loss was greater in the metformin group (-5.86% vs. 2.57%, p<0.05) and there was a significant reduction of plasma resistin levels in children with glucose intolerance, but no changes were reported in the concentration of other markers of inflammation [18].

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study included 699 subjects aged 10 to 17 years with T2DM of less than 2 years duration [19]. Subjects had HbA1c <8%, BMI ≥85th percentile, positive C-peptide and no evidence of pancreatic autoimmunity. Patients were randomly assigned to one of three arms: metformin alone, metformin plus rosiglitazone and metformin plus intensive lifestyle intervention, titrating metformin to 1000 mg twice daily and rosiglitazone to 4 mg twice daily [18]. After six months, the percent of subjects obtaining the weight loss target was significantly higher in the metformin plus lifestyle

intervention group (31.2%) than in the metformin plus rosiglitazone group (16.7%, p<0.001) but not significantly different from metformin alone (24.3%). In only half of the subjects, the treatment with metformin alone was effective in maintaining durable glycemic control while the addition of rosiglitazone to metformin, was superior to metformin alone and also superior to metformin and intensive lifestyle intervention. The results of TODAY study show that a majority of children with T2DM may require combination treatment (but metformin alone is approved for use in children) or insulin therapy within a few years after diagnosis [19].

Conclusions

Metformin is the most widely used drug for the treatment of T2DM in adults. In the same time, the use of metformin increases in pediatric age because of the worldwide surge in pediatric obesity and diabetes.

The current AAP guideline recommends to initiate lifestyle changes in diet and physical activity and to administrate metformin as the first-line therapy in youth with newly T2DM with mild hyperglycemia and without ketonuria or severe hyperglycemia. At present, the results of several studies show that the treatment with metformin is safe and not associated with severe complications in children and adolescents. In the same time, the efficacy of metformin for the treatment of polycystic ovary syndrome (PCOS) and T2DM in children is well demonstrated. However, only modest improvement in BMI in adolescents with obesity and normal glucose tolerance was observed so that there is no sufficient evidence to use metformin for the treatment of obesity or for the prevention of T2DM.

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