MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

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Abstract

Although there are many reports in the medical literature describing the therapeutic management of type 2 diabetes mellitus (T2DM), studies remain limited regarding the best approach of T2DM in children and adolescents. Even if in the last decade frequency of T2DM in children and adolescents has increased greatly in the world, this disease remains relatively uncommon in young people and the diagnosis is often hard to establish, sometimes even distinction from type 1 diabetes mellitus is difficult. On the other hand, adolescence is a time of important physiological and emotional changes that significantly complicate family interactions and adherence to treatment regimens. Long term safety and efficacy studies for pharmacologic agents are not available in children and adolescents with T2DM.

key words*: type 2 diabetes mellitus, children and adolescents, management.*

Management of T2DM in children and adolescents

T2DM is characterized by progressive beta cells failure and insulin resistance, manifested by high concentrations of plasma insulin and C peptide. In time, there is a progressive beta-cell failure and progressive loss of insulin secretory capacity [1].

In adolescents, there are significant differences between T2DM and type 1 diabetes [2]. The main differences relate to:

- *Age*. Unlike type 1 diabetes that occurs throughout childhood when parental influence is predominant, T2DM occurs typically in adolescence, when parents have less influence on their children, and peer influence predominates.

- *Family experience in diabetes treatment*. In adolescents with family history of T2DM, there can be members of the family that have experience with the disease, but there is a failure to control weight and glycemia, with resultant complications in the family members and a feeling of resignation and fatalism in the child.

- *Different treatment priorities*. Unlike type 1 diabetes, where insulin administration and glucose monitoring are essential, lifestyle modification being necessary only in those with overweight, in youth with T2DM, the emphasis is on lifestyle modification and secondarily on medication and glucose monitoring.

- *Effects of technology*. While recent technological advancements have

revolutionized the treatment of type 1 diabetes (insulin purity systems, the methods of insulin administration, blood glucose monitoring), other technological facilities from the last decades (fun sedentary ways, labor saving devices, easy access food with high caloric density and low price) are the main factors of T2DM in young people and raises great difficulties in managing this disease.

Given the underlying pathophysiology of insulin resistance, the initial approach to the treatment of T2DM generally focuses on improvement in insulin sensitivity, either through lifestyle habits modifications or through pharmacologic intervention.

Worldwide, obesity is increasing in all segments of the population. Prevention of T2DM requires prevention and treatment of overweight and obesity. Primary prevention of T2DM should be focused on optimizing the fetal environment in pregnancy; promoting breast-feeding; reversing wrong lifestyle, with excess caloric intake and marked decrease in energy expenditure by children in homes and communities [2].

The basic goals of T2DM therapy:

- Weight loss;
- Increase in exercise capacity;
- Normalization of glycemia;
- Control of co morbidities (hypertension, dyslipidemia, hepatic steatosis and nephropathy).

Treatment stages:

1. Education
   - Lifestyle modifications;
   - Diet;
   - Exercise;
   - Glycemic monitoring.
2. Pharmacologic agents

1. Education

Lifestyle change

Adolescent and family education is very important in T2DM, especially in terms of diet and physical activity.

Initial education efforts will focus on solving the causes of the disease, particularly overweight and sedentary lifestyle. These teenagers come mostly from families whose members are obese and with sedentary lifestyle. Therefore, it is very important that education should be done with the entire family, in a sustained manner, repeated at frequent intervals, otherwise, patients quickly resume their old habits [3, 4].

Although teenagers need autonomy and can take greater personal responsibilities, continuing family involvement in the management of adolescent patients with T2DM is necessary for optimum therapeutic results. Teenagers do not have the strength to persevere in the application of long term therapeutic measurements, if they are not supported.

The entire family will need education to understand the medical implications of obesity and T2DM.

The clinicians must understand the patient and family perceptions about health, so they can establish an effective behavioral plan.

Lifestyle changes should be made gradually, and the patient and family must understand that these changes need to be permanent.

Education will be performed by authorized persons (physician, nutritionist, psychologist, social worker) who will monitor the eating habits and physical activity [2].

Diet

Dietary management should include [5]:

- Limiting availability of high-fat, high caloric density food in the home;
- Complete elimination of sugar-containing soft drinks or artificial sweeteners for beverages, limited juice intake;
- Avoiding strict diets;
- Meals should be taken on schedule, in one place, with no other activity, preferably as a family unit;
- Meal portions with a limited amount of food/meal;
- Encouraging positive reinforcement of minor achievement and avoiding blame for failure.

Dietary measures should be introduced gradually by setting realistic goals, like moderate weight reduction rather than normalization of body weight, a goal that will quickly discourage patients.

However, it was found that even modest weight loss can markedly improve glycemic control and insulin resistance [6, 7].

Besides weight loss, dietary goals should include achieving optimum control of blood glucose, lipids and lipoproteins levels.

Some studies [8] showed that a ketogenic, very low calorie (VLCD) diet was effective in short-term treatment in pediatric patients with type 2 diabetes.

Both low-carbohydrate and low glycemic load diets have been shown to lead to greater weight loss in overweight adolescents than low-fat diets. However, these diets have not been studied specifically in children and young people with T2DM [9, 10, 11].

Exercise

As adolescents with T2DM are usually obese with low exercise tolerance, they should be encouraged to choose any physical activity they can accomplish with pleasure and on a routine basis, daily. There have not been reports comparing the efficacy of different types of physical activity for adolescents with T2DM.

But, it was found that increased daily physical activity or routine exercises led to a significant improvement of glycemic control in youth with T2DM, with favorable effects on improving insulin sensitivity and weight [1, 12, 13].

Using a pedometer may be motivating to patients and family members.

For the beginning, it is essential that the patient understands that it is very important to reduce the time spent in front of TV and computer related activities [2].

Glycemic monitoring

Self monitoring of blood glucose should be performed regularly, the frequency should be individualized and include a combination of fasting and postprandial glucose measurements.

HbA1c concentration should be determined at least twice a year, ideally would be quarterly.

2. Pharmacologic therapy

Initial treatment is determined by the presence of diabetes symptoms, the severity of hyperglycemia, and the presence or absence of ketosis/ketoacidosis.

Lifestyle changes regarding diet and physical activity are essential for increasing insulin sensitivity and should be

recommended to all adolescents diagnosed with T2DM. Pharmacologic therapy, if needed, will be used in combination with lifestyle interventions.

Until now, the currently available antidiabetic agents have not been adequately evaluated in pediatric patients. The goal of pharmacological treatment is to decrease insulin resistance, increase insulin secretion and to reduce postprandial glucose absorption.

Currently available oral hypoglycemic agents can be divided into three categories [1]:

– agents that improve insulin sensitivity: metformin, thiazolidinediones (TZDs),
– agents that stimulate insulin secretion: sulfonylureas, meglitinide analogs,
– glucosidase inhibitors that slow carbohydrate absorption: acarbose.

In addition to these agents, drugs that induce weight loss (orlistat, centrally acting adrenergic agents) may be considered relevant agents for the pharmacologic treatment of T2DM in adolescents [14].

More recently used new agents such as GLP-1 analogs and DPP-IV inhibitors may provide benefits for the treatment of T2DM in adolescents in the future, although there are currently no reported studies of their use in the pediatric population [1].

The drug of first intention in T2DM in adolescents should be metformin. It has the advantage over sulfonylureas of similar reduction in glycosylated hemoglobin, without the risk of hypoglycemia. In addition, during treatment with metformin weight is either decreased or remains stable; LDL-cholesterol and triglyceride levels are decreased [2].

Failure of monotherapy with metformin over 3 months indicates the need to add a glitazone, sulfonylurea or insulin as monotherapy or in combination with other pharmacological agents (meglitinide, amylin, a GLP-1 mimetic or a DPP-IV inhibitor).

Only metformin and insulin are approved for use in children and adolescents in the majority of countries. Sulfonylureas are approved for use in children in some countries, and other oral hypoglycemic agents can be used only in teenagers over 18 years.

Metformin decreases hepatic glucose production, gluconeogenesis and increases muscle glucose uptake. It has no effect on pancreatic insulin secretion and, therefore, requires the presence of insulin to be effective.

When endogenous secretion of insulin is adequate, as it is generally the case in T2DM, metformin can be used as a single agent to treat insulin resistance.

The advantages of using metformin as an initial agent in the treatment of type 2 diabetes include moderate weight loss through anorectic effect, a reduction in serum insulin concentration and improved lipid profile [15].

There are limited studies on the use of metformin in the pediatric population. In a study conducted by Jones and colleagues [16], a group of 82 cases aged 10-16 years with type 2 diabetes were treated with metformin at doses up to 1000 mg twice daily and it was found that metformin significantly improved both fasting plasma glucose and mean HbA1c values, compared with placebo; in addition, mean total serum cholesterol and body weight were decreased. The adverse effects more commonly reported were gastrointestinal discomfort (abdominal pain, diarrhea, vomiting), which are usually transient and can be avoided if the medication is taken with food and the dose is increased gradually. The

side effects may be attenuated by the use of extended release formulations [17, 18].

Insulin. Despite hyperinsulinemia and insulin resistance from T2DM, relatively small doses of supplemental insulin are often effective.

If there is an inadequate glycemic control on oral hypoglycemic agents, a long-acting insulin analogue may provide satisfactory therapy in combination with metformin, which improves insulin sensitivity. In adults with inadequately controlled T2DM, a single daily injection of insulin glargine was effective [2, 19]. Thiazolidinediones are not recommended in combination with insulin because of increased risk of fluid retention. If postprandial hyperglycemia occurs, insulin may be associated with pre-meal meglitinide.

It has been found that a large number of adolescents with new onset of T2DM were treated with insulin because the initial diagnosis is often unclear. In addition, patients with severe hyperglycemia, ketosis or ketoacidosis, require insulin to correct metabolic imbalances. In a study by Silverstein et al. (2000), 40-50% of the children with T2DM were initially treated with insulin [20]. But there are no long-term prospective studies, in children and adolescents with T2DM, comparing glycemic control, hypoglycemia, compliance and quality of life between patients treated with oral hypoglycemic agents and insulin.

Sulfonylureas and meglitinide/repaglinide are insulin secretagogues, and they are not approved under 18 years.

Sulfonylureas increase insulin secretion by interaction with K+/ATP channels in the pancreatic beta cells membrane, the effect being prolonged [1, 22].

Meglitinide analogs bind also on the K+/ATP channel, but these act on a different binding site than that of the sulfonylureas, and have quicker response and shorter duration [22, 23].

The adverse effects of these drugs are the increased risk of hypoglycemia and weight gain.

Thiazolidinediones (**Pioglitazone**) are only approved for use in adults [24, 25, 26].

They are indicated for monotherapy or for use in combination with a sulfonylurea, metformin or insulin in adults with T2DM. These are selective agonists for PPAR gamma receptors, activation of these receptors resulting in increased glucose transport into cells in adipose tissue, muscle and liver.

There have been studies that included adolescents aged 12 to 17 with T2DM in which the pharmacokinetic profile, safety, and tolerability of thiazolidinediones have been studied. Favorable pharmacokinetic properties and safety profile are encouraging for further studies regarding the use of pioglitazone in adolescents.

Side effects include weight gain, fluid retention, anemia, increased liver enzyme levels and an increased risk of heart disease in adults.

Glucosidase inhibitors (**Acarbose** and **Miglitol**) are only approved for use in adults.

These are alpha glucosidase inhibitors, which reduce the absorption of carbohydrates in the small intestine by inhibiting breakdown of oligosaccharides and delaying their absorption, which facilitates better postprandial blood glucose control.

These are recommended for adults with impaired glucose tolerance, in combination

with changes in lifestyle, delaying the development of T2DM.

There are predominantly gastrointestinal side effects (flatulence, abdominal pain, diarrhea) due to the osmotic effect of oligosaccharides and bacterial fermentation [1, 27, 28].

Amylin is not recommended for those under 18 years and is only approved for use in the United States for patients with type 1 diabetes and T2DM who are taking insulin. It is administered by subcutaneous injections before meals.

Amylin is a peptide that is co-secreted with insulin from pancreatic beta cells in response to food intake. The blood glucose lowering effect is achieved by reducing glucagon release, slowing gastric emptying and decreasing food intake. The main side effect is hypoglycemia.

There are reported studies of amylin use in children with type 1 diabetes [2, 29].

Incretin mimetics, glucagon-like peptide 1 receptor (GLP-1) agonists, are only approved for use in adults [2].

GLP-1 is rapidly secreted by L cells in the small intestine in response to food intake, increasing insulin secretion proportionate to blood glucose concentrations, suppressing the secretion of glucagon, prolonging gastric emptying and promoting satiety. It is rapidly degraded by dipeptidyl peptidase IV (DPP IV).

It acts by reducing fasting and postprandial blood glucose and lower HbA1c. Side effects are mainly gastrointestinal.

DPP-IV inhibitors are only approved for use in adults; they inhibit the DPP-IV enzyme that breaks down GLP-1, producing effects similar to those of GLP-1 mimetics. They are administered orally in association with metformin or a thiazolidinedione once daily.

Combining oral hypoglycemic agents [1]

In T2DM, a disease with multifactorial etiology, monotherapy is likely to be insufficient in some cases. When a single oral hypoglycemic agent cannot achieve acceptable glycemic control, an additional agent may be needed. It is preferred a combination of two hypoglycemic drugs with different mechanisms of action. Various combinations have been studied in adults, such as: metformin/sulfonylurea, metformin/TZDs, metformin/meglitinide, TZDs/sulfonylureas or TZDs/meglitinide, but there are no published studies of combination therapy in children and adolescents.

There are some disagreements about the optimal approach to combination therapy and, also, about whether a single agent should be titrated to maximal dose or whether synergistic effects can be obtained by association of the second drug, but with preservation of lower doses.

Long-term monitoring of T2DM requires frequent visits to the doctor, initially every 2-4 weeks, then every 2-3 months for education and family support to establish weight loss. Home blood glucose monitoring in patients that are not on insulin is sufficient to be performed twice a day (fasting and 2 hours postprandial) and more often when there are intercurrent diseases. HbA1c should be determined at each visit with a target of keeping it below 6.5%.

Because of increased risk of early-onset of diabetes complications in T2DM, monitoring blood pressure should be performed, as well as

evaluation at diagnosis and then annually for dyslipidemia, microalbuminuria and retinopathy. There is a need for early diagnosis of obesity–related comorbidities: non-alcoholic fatty liver disease, eating disorders, depression and sleep apnea.

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