TYPE 2 DIABETES AND METABOLIC SYNDROME IN OBESE CHILDREN – A REALITY

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Abstract

By the end of the 20th century the incidence of type 2 diabetes mellitus (T2DM) in children had increased dramatically. Once considered a disease of the overweight, middle age person, the incidence of type 2 diabetes is rising rapidly in children and adolescents worldwide, with the highest prevalence in those of American−Indian, Hispanic, African−American, and Asian descent (1,2). The alarming incidence and prevalence of diabetes has been attributed to increasing obesity among younger people (3). The hallmark of type 2 diabetes in the young, as in most adults, is insulin resistance (4, 5). On a global basis, the rise in T2DM rates mirrors the growth in urbanization and economic development – obesity appears to be the key link (6, 7).

Key words: childhood, diabetes, obesity, insulino-resistance.

Introduction

T2DM occurs when insulin secretion is inadequate to meet the increased demand posed by insulin resistance (8). T2DM is commonly associated with other features of the insulin resistance syndrome (hyperlipidemia, hypertension, acanthosis nigricans, ovarian hyperandrogenism, non-alcoholic fatty liver disease -NAFLD) (9).

Diagnosis of type 2 diabetes (10):

Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of symptoms (11, 12). Diabetes is diagnosed when:

• A fasting plasma glucose **(FPG)** is ≥ 7.0 mmol/l (126 mg/dl) **or**

• The post challenge plasma glucose is >11.1 mmol/l (200 mg.dl) **or**

• Symptoms of diabetes and a casual plasma glucose ≥ 200 mg/dl (11.1 mmol/L).

Previously, the majority of cases of diabetes in the pediatric population have been type 1. However, the increasing incidence of type 2 diabetes in this population presents a challenge to the clinician, who must be able to distinguish between type 1 and type 2 diabetes in children, to optimize therapy (Table 1).

- with increasing obesity in childhood, as many as 15–25% of newly diagnosed T1DM (or monogenic diabetes) patients may be obese.
- the significant number of pediatric patients with T2DM demonstrating ketonuria or ketoacidosis at diagnosis
- There is considerable overlap in insulin or C-peptide measurements between T1DM, T2DM and MODY at onset of diabetes and over the first year or so. The role of C peptide may be more helpful in established diabetes as persistent elevation of C-peptide above the level of normal would be unusual in T1DM after 12–24 months.

Table 1. Major characteristics of T1DM/T2DM/MODY

	T1DM	T2DM	MODY
Genetics	poligenic	poligenic	monogenic
Age at onset	6 months to young adulthood	Mean age 12-14 years	Often post pubertal
Course	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable
Autoimmunity	Yes	No	No
Obesity	Population frequency	Increased frequency	Population frequency
Achantosis nigricanns	No	Yes	No
Parent with diabestes	2-4 %	80 %	90 %

The American Diabetes Association recommends screening for diabetes among children with a BMI of > 85th percentile for age and gender, with 2 additional risk factors for T2DM (Table 2).

Table 2. Testing Guidelines for T2DM

Overweight or at risk for overweight ➢ BMI >85th percentile for age and gender; or ➢ Body weight for height >85th percentile; or ➢ Body weight >120% of ideal for height
+ Plus any 2 of the following
➢ Family history of T2DM in first- or second-degree relatives ➢ Race/ethnicity (American Indian, black, Hispanic, Asian/Pacific Islander) ➢ Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome) ➢ Age of screening initiation: 10 y or at onset of puberty if puberty occurs at a younger age
➢ Frequency of testing: Every 2 years ➢ Test: Fasting plasma glucose (OGTT can also be used to confirm diabetes)

T2DM and the insulin resistance syndrome

Insulin resistance is an impaired response to the physiologic effects of insulin, including effects on glucose, lipid, and protein metabolism, and on vascular endothelial function.

Glucose homeostasis is maintained by insulin secretion, insulin action, hepatic glucose production, and cellular glucose uptake (13).

The onset of puberty also contributes to insulin resistance, with insulin sensitivity decreasing by approximately 30% and compensatory increases in insulin secretion (14, 15). All children become more insulin resistant at the time of puberty. Insulin resistance increases immediately at the beginning of puberty, peaks at mid-puberty, and then declines to nearly prepubertal levels by early adulthood. Girls are more insulin resistant than boys during puberty which is related in part to differences in adiposity between the sexes. Growth hormone has been considered a contributing factor in the development of insulin resistance during puberty, with an inverse correlation between growth hormone levels and insulin action

Diabetes is only one manifestation of the insulin resistance syndrome or the MS (metabolic syndrome). Other associations include:

- Obesity
- Hypertension
- Nephropaty (albuminuria)
- Dyslipidemia (Hypertriglyceridemia and decreased high-density lipoprotein cholesterol)
- Ovarian hyperandrogenism and premature adrenarche (16)
- NAFLD (non-alcoholic fatty liver disease): Hepatic steatosis is present in 25–45% of adolescents with T2DM
- Systemic inflammation: elevated C-reactive protein, inflammatory cytokines in obese adolescents have been associated with increased risk for cardiovascular disease in adults (17).

Management goals in obese - diabetics childs :

• Weight loss
• Increase in exercise capacity
• Normalization of glycemia
• Control of comorbidities: including hypertension, dyslipidemia, nephropathy, and hepatic steatosis

Treatment which includes physical activity and a well balanced diet, with the appropriate amount of carbohydrates and protein to maintain a healthy weight, is vital. Further studies evaluating the long-term benefit of diet and exercise should be conducted in children and adolescents (19).

Pharmacologic therapy should be implemented if glycemic goals are not achieved through proper diet and increased physical activity (maintaining euglycemia with metformin, sulfonylureas, thiazolinediones, and insulin is recommended). – Table 4.

- The first medication used should be metformin (20). Metformin acts on insulin receptors in liver, muscle, and fat tissue, with a predominant action on the liver. An initial anorexic effect may promote weight loss. Long-term use is associated with a 1–2% reduction in HbA1c. Intestinal side effects (transient abdominal pain, diarrhea, nausea) may occur. It has the advantage over sulfonylureas of similar reduction in HbA1c without the risk of hypoglycemia. Despite hyperinsulinemia and insulin resistance, relatively small doses of supplemental insulin are often effective. If glycemic control on oral agents is inadequate, a long-acting insulin analogue may provide satisfactory therapy without meal related therapy. Metformin should be continued to improve insulin sensitivity (21).

Table 3*:* A range of the published metabolic syndrome definitions in pediatrics (18).

	Three or more of the following				
	Cook et al. *Arch Pediatr Adolesc Med*, 2003; 157, 821-74	de Ferranti et al. *Circulation*, 2004; 110, 2494-721	Cruz et al. *J Clin Endocrinol Metab*, 2004; 89, 108-1322	Weiss et al. *N Engl J Med*, 2004; 350, 2362-743	Ford et al. *Diabetes Care*, 2005; 28, 878-8144
1.	Fasting glucose ≥110 mg/dL	Fasting glucose ≥6.1 mmol/L (≥110 mg/dL)	Impaired glucose tolerance (ADA criterion)	Impaired glucose tolerance (ADA criterion)	Fasting glucose ≥110 mg/dL (additional analysis with ≥100 mg/dL)
2.	WC ≥90th percentile (age- and sex-specific, NHANES III)	WC >75th percentile	WC ≥90th percentile (age-, sex- and race-specific, NHANES III)	BMI –Z score ≥2.0 (age- and sex-specific)	WC ≥90th percentile (sex-specific, NHANES III)
3.	Triglycerides ≥110 mg/dL (age-specific, NCEP)	Triglycerides ≥1.1 mmol/L (≥100 mg/dL)	Triglycerides ≥90th percentile (age- and sex-specific, NHANES III)	Triglycerides >95th percentile (age-, sex- and race-specific, NGHS)	Triglycerides ≥110 mg/dL (age-specific, NCEP)
4.	HDL-C ≤40 mg/dL (all ages/ sexes, NCEP)	HDL-C <1.3 mmol/L (<50 mg/dL)	HDL-C ≤10th percentile (age- and sex-specific, NHANES III)	HDL-C <5th percentile (age-, sex- and race-specific, NGHS)	HDL-C ≤40 mg/dL (all ages/ sexes, NCEP)
5.	Blood pressure ≥90th percentile (age-, sex- and height-specific, NHBPEP)	Blood pressure >90th percentile	Blood pressure >90th percentile (age-, sex- and height-specific, NHBPEP)	Blood pressure >90th percentile (age-, sex- and height-specific, NHBPEP)	Blood pressure >90th percentile (age-, sex- and height-specific, NHBPEP)

Table 4. Oral antidiabetics.

Oral antidiabetics	Mechanism of Action	Side Effects
INSULINSENZITIZERS		
Biguanides Metformin (the drug of first choice)	Decrease hepatic glucose production Increase muscle glucose uptake and utilization	Nausea Diarrhea Anorexia Lactic acidosis
Thiazolidinedinediones Rosiglitazone Pioglitazone	Increase insulin sensitivity via activation of PPAR-g receptors	Fluid retention and weight gain
INSULIN SECRETAGOGUES		
Sulfonylureas Glimiperide (Amaryl) Glipizide Tolbutamide Chlorpropamide Tolazamide	Stimulate first-phase insulin secretion by blocking K+ channel in ß-cells	Late hyperinsulinemia and hypoglycemia Weight gain
OTHERS		
Meglitinides Repaglinide Nateglinide	Stimulate first-phase insulin secretion by blocking K+ channel in ß-cells	Hypoglycemia Weight gain
a-Glucoside Inhibitors Acarbose Miglitol	Decrease hepatic glucose production Delays glucose absorption	Flatulence Abdominal bloating

Conclusion

Environmental factors, such as increased caloric intake combined with a sedentary lifestyle, have contributed to obesity and insulin resistance; the key players in the pathogenesis of type 2 diabetes in the young

Because type 2 diabetes is increasing at alarming rates in children and adolescents, all health care providers must play an active role in providing education regarding proper nutrition, physical activity, and pharmacologic therapy to patients.

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