Vitamins & Minerals

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Double Diabetes: The Evolving Treatment Paradigm in Children and Adolescents

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Background

Diabetes mellitus is one of the most prevalent chronic diseases in children and adolescents; about 151,000 people below the age of 20 have diabetes [1]. Poorly controlled diabetes mellitus predisposes children and adolescents to acute and chronic complications. Adults with diabetes have a ten-fold increase in the risk of cardiovascular disease as compared to the general population [2]. These complications place a heavy burden on the national healthcare budget.

Diabetes mellitus is classified into four major types: type 1, type 2, gestational, and other specific types, for example, cystic fibrosis-related diabetes. Type 1 diabetes (T1D) is caused by autoimmune destruction of the beta cells of the pancreas leading to insulinopenia [3]. Type 2 diabetes (T2D) results from a combination of Insulin Resistance (IR) and beta cell insulin secretory insufficiency. The rising incidence of obesity has made it more difficult to differentiate between these types of diabetes in children. There is a new variant of diabetes in children designated as double diabetes, or hybrid diabetes, in which both T1D (antibody positivity) and T2D (insulin resistance and insufficiency) co-exist in the same individual (Figure 1).

Childhood obesity is one of the most serious public health challenges of the 21st century [4]. According to the National Health and Nutrition Examination Survey data, about 16% of children and adolescents in the United States are obese with a Body Mass Index (BMI) (kg/m^2) ≥ 95th percentile for age and gender [5-8] with the highest percentages in teens. The prevalence of obesity has tripled in the past three decades [9] among male and female adolescents, and across many racial and ethnic groups [10,11]. Although obesity is associated primarily with T2D due to IR [12], it may also impact T1D morbidity and phenotype by causing earlier exhaustion of the beta cells through IR.

A new subset of diabetes mellitus, known as double diabetes**,** is becoming increasingly prevalent as a result of the epidemic of childhood obesity [13-15]. In double diabetes, elements of both T1D and T2D co-exist. In this condition, individuals with T1D have insensitivity to insulin that is most often associated with obesity; and individuals thought to have T2D have diabetes-associated autoantibodies against the pancreatic beta cells [12]. The prevalence of double diabetes is unknown [13] however, about 25% of children with T1D are either overweight or obese [16]. Conversely, about 35% of children and adolescents with T2D have at least one diabetes-associated antibody [17].

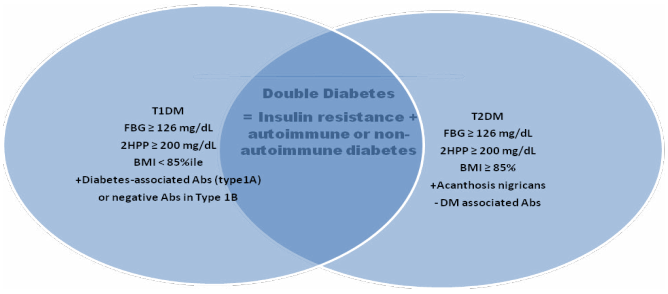
The availability of insulin analogs and insulin delivery devices has improved diabetes management in the US. However, according to recent studies, the prevalence of poorly-controlled diabetes in youth is still high [1]. A report by the SEARCH for Diabetes in Youth Study group showed that a high proportion of youth with diabetes had elevated HbA1c levels, with 17% of the youth with TIDM, and 27% of those with T2D showing poor control, defined as HbA1c ≥ 9.5%. The physiological factors that contribute to poor glycemic control in youth are in part related to the hormonal changes in puberty, which may lead to weight gain. Puberty is associated with relative IR, as reflected in a two to threefold increase in the peak insulin response to oral or intravenous glucose [18], as well as an insulin-mediated glucose disposal that is approximately 30% lower in adolescents than in pre-pubertal children or young adults [19]. Evidence for the coexistence of IR and insulin deficiency in childhood-onset T1D adults has also been demonstrated by the insulin-glucose clamp technique [20,21]. The increasing IR, obesity, and deterioration of glycemic control in adolescents create a great need for alternative therapeutic strategies in adolescents with double diabetes.

Lack of Consensus on Therapeutic Modalities for Double Diabetes

There is no consensus for the best therapeutic regimen for children and adolescents with double diabetes. However, because IR is central to its pathophysiological mechanism, optimal management necessitates the addition of insulin sensitizers under appropriate clinical circumstances to the patient's therapeutic regimen [15]. Intensification of lifestyle modification strategies should be encouraged to maintain normal weight and attenuate IR. Finally, because these patients require increased doses of insulin to maintain euglycemia, it is necessary to develop an insulin titration regimen that would ensure adequate glycemic control.

The Need for Adjunctive Metformin Regimen for Double Diabetes

In general, patients with double diabetes are overweight or obese and the resultant IR increases their exogenous insulin requirement [4]. However, unlike T1D and T2D, there is no consensus for the



TID=type 1 diabetes, T2D=type 2 diabetes, FBG=fasting blood glucose, 2HPP=2 hour post prandial glucose level; BMI=body mass index; Abs=antibodies

Figure 1: The Relationship between type 1, type 2, and double diabetes.

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best therapeutic regimen for children and adolescents with double diabetes. One such strategy is the addition of a drug that increases insulin sensitivity such as metformin, a biguanide that acts principally in the liver by inhibiting hepatic gluconeogenesis and thereby reducing hepatic glucose production [22]. Metformin is approved by the Food and Drug Administration for use in children with T2D, and recently it has been recommended that metformin added to insulin therapy might be used in clinical practice in adolescents with T1D who are poorly controlled and show evidence of IR (double diabetes) as noted in T2D [23].

Given the rising prevalence of obesity in the general population we speculate that many children with T1D will eventually also become insulin resistant. The coexistence of both T1D and T2D in an individual should in principle denote an increased risk for the complications of both conditions [24] . Therefore, it is possible that these individuals are at higher risk for both the microvascular and metabolic complications of T1D and the macrovascular complications of T2D [15]. Such a double-hit effect will result in poorer health outcomes, and put increased pressure on the national healthcare budget. Thus, it is timely to devise an appropriate management protocol to improve glycemic control in this burgeoning sub-population.

Because of the paucity of data on the role of adjunctive metformin therapy in children and adolescents with double diabetes, our group at the University of Massachusetts is conducting a randomized, double-blind, placebo-controlled trial to evaluate the effect of adjunctive metformin therapy in children and adolescents with double diabetes.

The Need for an Insulin Titration Regimen for Double Diabetes

Another therapeutic modality for individuals with double diabetes is the exploration of optimal insulin titration regimen to ensure euglycemia. Patients with double diabetes are overweight or obese and the resultant IR increases their insulin requirement [4]. However, in addition to requiring a high insulin dose, evidence suggests that many patients often do not have the insulin doses titrated sufficiently to achieve target levels of glucose control [25,26]. These patients remain on suboptimal doses of insulin and fail to reach treatment targets [27]**.** In a recent study Blonde et al. [27] demonstrated the efficacy of algorithm-guided, patient titration of once daily long acting insulin in normalizing HbA1c in adult patients with T2D. Our group is also conducting a randomized control trial to explore the role of protocol-driven treat-to-target regimen in children and adolescents with double diabetes. Specifically, we will investigate whether a titrated insulin regimen alone would have a superior-or similar effect to combined metformin and titrated insulin regimen in children and adolescents with double diabetes and how this combination of treatment compares to standard insulin therapy.

In conclusion, the global pandemic of obesity in children and adolescents has resulted in a new expression of diabetes mellitus designated as double diabetes. The entity encompasses the autoimmune load of T1D and the metabolic load of T2D. There is no consensus on the best therapeutic modality for this new expression of diabetes mellitus. Optimal therapeutic options must address the coexistence of both metabolic and autoimmune components of diabetes mellitus in the patient. There have also been calls to revise the current classification of diabetes mellitus to take into account the surging prevalence of double diabetes in children and adolescents.

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