

1-18-2013

# Double Diabetes: The Evolving Treatment Paradigm in Children and Adolescents

Benjamin U. Nwosu

*University of Massachusetts Medical School*

Follow this and additional works at: [http://escholarship.umassmed.edu/peds\\_endocrinology](http://escholarship.umassmed.edu/peds_endocrinology)



Part of the [Endocrine System Diseases Commons](#), [Endocrinology, Diabetes, and Metabolism Commons](#), and the [Pediatrics Commons](#)

---

## Repository Citation

Nwosu, Benjamin U., "Double Diabetes: The Evolving Treatment Paradigm in Children and Adolescents" (2013). *Endocrinology/Diabetes*. 39.

[http://escholarship.umassmed.edu/peds\\_endocrinology/39](http://escholarship.umassmed.edu/peds_endocrinology/39)

This material is brought to you by eScholarship@UMMS. It has been accepted for inclusion in Endocrinology/Diabetes by an authorized administrator of eScholarship@UMMS. For more information, please contact [Lisa.Palmer@umassmed.edu](mailto:Lisa.Palmer@umassmed.edu).

# Double Diabetes: The Evolving Treatment Paradigm in Children and Adolescents

Benjamin U Nwosu\*

Department of Pediatrics, University of Massachusetts Medical School, USA

## 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 21<sup>st</sup> 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) ( $\text{kg}/\text{m}^2$ )  $\geq$  95<sup>th</sup> 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 T1DM, and 27% of those with T2D showing poor control, defined as HbA1c  $\geq$  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-

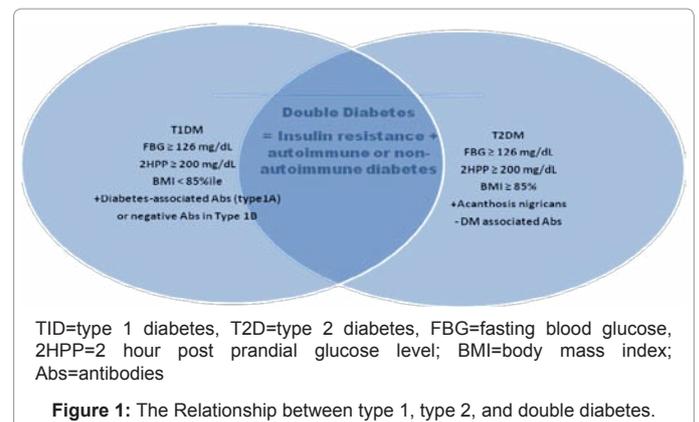
pubertal children or young adults [19]. Evidence for the coexistence of IR and insulin deficiency in childhood-onset T1D adults has also been demonstrated by the insulin-glucose clamp technique [20,21]. The increasing IR, obesity, and deterioration of glycemic control in adolescents create a great need 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



\*Corresponding author: Benjamin U Nwosu, Department of Pediatrics, University of Massachusetts Medical School, USA, E-mail: [Benjamin.Nwosu@umassmemorial.org](mailto:Benjamin.Nwosu@umassmemorial.org)

Received January 09, 2013; Accepted January 12, 2013; Published January 18, 2013

Citation: Nwosu BU (2013) Double Diabetes: The Evolving Treatment Paradigm in Children and Adolescents. Vitam Trace Elem 2: e118. doi:10.4172/2167-0390.1000e118

Copyright: © 2013 Nwosu BU. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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.

## References

1. Petitti DB, Klingensmith GJ, Bell RA, Andrews JS, Dabelea D, et al (2009)

Glycemic Control in Youth with Diabetes: the SEARCH for Diabetes in Youth Study. *J Pediatr* 155: 668-672.

2. Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, et al (2003) Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. *Diabetologia* 46 : 760-765.
3. Pickup JC, Williams, G (2002) *Textbook of Diabetes Vol 2*. 3<sup>rd</sup> ed: Blackwell Publishing.
4. Pozzilli P, Guglielmi C, Caprio S, Buzzetti R (2011) Obesity, autoimmunity, and double diabetes in youth. *Diabetes Care* 2: S166-170.
5. Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, et al. (2004) Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. *JAMA* 291: 2847-2850.
6. Flegal KM, Wei R, Ogden C (2002) Weight-for-stature compared with body mass index-for-age growth charts for the United States from the Centers for Disease Control and Prevention. *Am J Clin Nutr* 75: 761-766.
7. Himes JH, Dietz WH (1994) Guidelines for overweight in adolescent preventive services: recommendations from an expert committee. The Expert Committee on Clinical Guidelines for Overweight in Adolescent Preventive Services. *Am J Clin Nutr*. 59: 307-316.
8. Flodmark CE, Lissau I, Moreno LA, Pietrobelli A, Widhalm K (2004) New insights into the field of children and adolescents' obesity: the European perspective. *Int J Obes Relat Metab Disord* 28: 1189-1196.
9. Ogden CL, Flegal KM, Carroll MD, Johnson CL (2002) Prevalence and trends in overweight among US children and adolescents, 1999-2000. *JAMA* 288: 1728-1732.
10. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, et al. (2006) Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA* 295: 1549-1555.
11. Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL (1995) Overweight prevalence and trends for children and adolescents. The National Health and Nutrition Examination Surveys, 1963 to 1991. *Arch Pediatr Adolesc Med* 149: 1085-1091.
12. Kaufman F (2006) 'Double diabetes' in young people and how to treat it. *Diabetes Voice* 51:19-22.
13. Pozzilli P, Guglielmi C (2009) Double diabetes: a mixture of type 1 and type 2 diabetes in youth. *Endocr Dev* 14: 151-166.
14. Reinehr T, Schober E, Wiegand S, Thon A, Holl R, et al. (2006) Beta-cell autoantibodies in children with type 2 diabetes mellitus: subgroup or misclassification?. *Arch Dis Child* 91: 473-477.
15. Libman IM, Becker DJ (2003) Coexistence of type 1 and type 2 diabetes mellitus: "double" diabetes? *Pediatr Diabetes* 4: 110-113.
16. Yki-Jarvinen H (1997) Acute and chronic effects of hyperglycaemia on glucose metabolism: implications for the development of new therapies. *Diabet Med* 3: S32-37.
17. Hathout EH, Thomas W, El-Shahawy M, Nahab F, Mace JW (2001) Diabetic autoimmune markers in children and adolescents with type 2 diabetes. *Pediatrics* 107: E102.
18. Rosenbloom AL, Wheeler L, Bianchi R, Chin FT, Tiwary CM, et al. (1975) Age-adjusted analysis of insulin responses during normal and abnormal glucose tolerance tests in children and adolescents. *Diabetes*. 24: 820-828.
19. Caprio S, Tamborlane WV (1999) Metabolic impact of obesity in childhood. *Endocrinol Metab Clin North Am* 28: 731-747.
20. Erbey JR, Kuller LH, Becker DJ, Orchard TJ (1998) The association between a family history of type 2 diabetes and coronary artery disease in a type 1 diabetes population. *Diabetes Care* 21: 610-614.
21. Williams KV, Erbey JR, Becker D, Arslanian S, Orchard TJ (2000) Can clinical factors estimate insulin resistance in type 1 diabetes? *Diabetes* 49: 626-632.
22. Hamilton J, Cummings E, Zdravkovic V, Finegood D, Daneman D (2003) Metformin as an adjunct therapy in adolescents with type 1 diabetes and insulin resistance: a randomized controlled trial. *Diabetes Care* 26: 138-143.
23. Abdelghaffar S, Attia AM (2009) Metformin added to insulin therapy for type 1 diabetes mellitus in adolescents. *Cochrane Database Syst Rev* : CD006691.
24. Pozzilli P, Guglielmi C, Pronina E, Petraikina E (2007) Double or hybrid

diabetes associated with an increase in type 1 and type 2 diabetes in children and youths. *Pediatr Diabetes* 9: 88-95.

25. (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352: 837-853.

26. Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R (2005) Improvement

of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. *Diabetes Care* 28: 1282-1288.

27. Blonde L, Merilainen M, Karwe V, Raskin P (2009) Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets - the TITRATE study. *Diabetes Obes Metab* 11: 623-631.

**Citation:** Nwosu BU (2013) Double Diabetes: The Evolving Treatment Paradigm in Children and Adolescents. Vitam Trace Elem 2: e118.  
doi:[10.4172/2167-0390.1000e118](https://doi.org/10.4172/2167-0390.1000e118)

### Submit your next manuscript and get advantages of OMICS Group submissions

#### Unique features:

- User friendly/feasible website-translation of your paper to 50 world's leading languages
- Audio Version of published paper
- Digital articles to share and explore

#### Special features:

- 250 Open Access Journals
- 20,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, DOAJ, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://omicsgroup.info/editorialtracking/vitamins/>

