

New-Onset Diabetes in Obese Adolescents – Type 1 or Type 2 Diabetes? Comparative Cases Report

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Abstract

The increasingly obesogenic environment exerts a ponderous impact on the clinical presentation and the course of diabetes. Obesity is strongly linked to T2DM development, yet, the latest observation has shown that more cases of T1DM are diagnosed in youth who had been obese before the onset of the disease. What is more, the presence of autoimmunity is noticed in patients phenotypically classified as T2DM. The overlap of the clinical phenotypes of diabetes has become a new challenge for physicians who formulate a differential diagnosis. There is a question to consider how such patients should be classified. Not to discount the importance of identifying diabetes in an obese child, it is the therapeutic approach to such a complex patient that a physician should mainly focus on. Cases presented herein address the role that childhood obesity plays in making a differential diagnosis of diabetes and even more in choosing the adequate therapy.

Keywords: Obesity; T1DM; T2DM; Double diabetes; LADY; Diagnosis; Diabetes autoantibodies; treatment

Abbreviations: T1DM: Type 1 Diabetes; T2DM: Type 2 Diabetes; LADY: Latent Autoimmune Diabetes in Youth; LADA: Latent Autoimmune Diabetes in Adults; CS: Caesarean Section; SVD: Spontaneous Vaginal Delivery; HT: Hypertension; BMI: Body Mass Index; A1c: Glycated Hemoglobin; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; IAA: Anti-Insulin Antibodies; GAD: Glutamic Acid Decarboxylase Antibodies; IA2: Tyrosine Phosphatase-like Protein Antibodies; aTPO: Anti-Thyroperoxidase Antibodies; aTG: Anti-Thyroglobulin Antibodies; TSH: Thyroid-Stimulating Hormone; FT4: Free Thyroxine; USG: Ultrasound; RBG: Random Blood Glucose; FPG: Fasting Plasma Glucose; GP: General Practitioner; TDI: Total Daily Insulin; OID: Once a Day; TID: Twice a Day; APS III: Autoimmune Polyendocrine Syndrome III; ISPAD: The International Society for Pediatric and Adolescent Diabetes; CDC: Centers for Disease Control and Prevention; DASP: Diabetes Antibody Standardization Program; RIA: Radioimmunoassay

Introduction

Having been facing the progressive increase in the prevalence of childhood obesity in both the industrialized and developing countries, an overlap of the clinical phenotypes of diabetes is frequently witnessed, making it increasingly challenging to differentiate among the types of the disease. Childhood obesity has become one of the most serious public health challenges of the 21st century. Currently 10% of children worldwide are either overweight or obese, with the increasing weight gain affecting over 42 million of those under the age of 5 years [1,2]. Although in Europe the prevalence of childhood obesity still tends to be lower than in the US, the gap between these two continents is noticeably narrowing [3,4]. It is especially visible in Poland and England, where a recent report conducted by International Obesity Task Force (March 2005) has shown the steepest increase in the prevalence of obesity among children aged 5-11 years [5].

The current epidemiological data also indicate a marked increase in the prevalence of T1DM in childhood population worldwide. The number of diabetic children aged 0-14 years is estimated to be 490.1 thousands. The rise of incidence of T1DM has been witnessed over the past decades, with younger patients accounting for the majority of newly

diagnosed cases. An annual increase of the incidence equals 3% [6]. Moreover, it has recently become apparent that more cases of T1DM are diagnosed in children and adolescents who had been overweight or even obese before the onset of the disease [7,8]. Furthermore, the obesogenic environment has been associated with the increasing prevalence of T2DM in the younger age groups, which until recently was rarely diagnosed in children [9-11]. Although obesity is strongly linked to T2DM development, latest data have shown that it also plays a significant role and exerts its effects on other types of diabetes.

Moreover, obesity has changed the clinical presentation and the course of diabetes. For these reasons, both phenotypic characteristics and clinical presentation of different types of the disease have dramatically altered. Both the changing phenotype of T1DM in the youth and the increasing prevalence of T2DM in childhood population have become a new challenge for physicians who make a differential diagnosis of diabetes and especially for its further therapy.

The authors hereof present a comparison of two obese adolescents who presented a different clinical manifestation at the onset of diabetes mellitus.

Cases Presentation

Case 1

A 14-yr-old boy presented to the Department of Pediatric Diabetes with a 1-month history of polydipsia and polyuria. In the three months leading up to the presentation he had undergone an unintentional weight loss of ~8 kg.

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The patient was born on term by CS (due to cross-birth) following an uncomplicated pregnancy. His birth weight was 3200 g, Apgar scores 10. His prenatal history was unremarkable. He has been obese since the age of 6 yr but was otherwise healthy and receiving no medication. Family history was positive for T2DM (maternal grandfather and paternal grand-mother), HT (mother) and obesity (paternal grandparents).

On admission his body weight was 113 kg (>97 percentile) and height was 173 cm (50-75 percentile), yielding a BMI of 37.1 kg/m², well above the 97th percentile for his age and gender in accordance with Polish 2010 growth references for school-aged children and adolescents by Kułaga et al. [12]. The obesity was generalized, and there was no acanthosis nigricans. Pubertal stage was Tanner 3/4.

Laboratory work-up: Laboratory work-up was remarkable for hyperglycemia (347 mg/dl; 19.2 mmol/l), elevated A1c (13.1%; 120 mmol/mol), and the urinalysis revealed both glucosuria (> 1,000 mg/dl) and ketonuria (>80 mg/dl). Fasting lipid profile showed decreased HDL and increased LDL levels (21 mg/dl and 145 mg/dl, respectively). Liver and kidney tests were both normal. Before the onset of medical therapy fasting insulin and c-peptide levels were 5.1 uU/ml and 1.21 pmol/ml, respectively. Autoantibodies IAA, GAD and IA2 were weakly positive (Table 1).

Treatment and follow-up: The tentative diagnosis was T1DM, and treatment with insulin (~0.3U/kg/day) as well as diet and exercise were initiated. Within one month, the patient's BMI dropped to 35.5 kg/m² and he achieved glycemic goals requiring decreased insulin doses (~0.1 U/kg/day). During the course of the next 4 months, patient's BMI decreased to 33.9 kg/m² after the first 6 weeks and further down to 30.4 kg/m² after the next 12 weeks. During that period insulin was discontinued from his regimen. He maintained good metabolic control (A1c 5.6%; 38 mmol/mol) following recommendations regarding diet and increased physical activity in accordance with ISPAD guidelines [13] (Table 2).

Case 2

A 17-yr-old girl was referred to Diabetes Outpatients Clinic by GP due to elevated fasting plasma glucose level (108-110 mg/dl; 6.0-6.1 mmol/l) in generally good condition.

The patient was born on term by SVD following an uncomplicated

pregnancy. Her birth weight was 2950 grams, Apgar scores 10. Her prenatal history was unremarkable. She has been overweight since early childhood, with rapid progression to obesity during pubertal period. The girl did not present symptoms of T1DM such as polyuria, polydipsia and weight loss. She did not have any coexisting disorders. Family history was negative for diabetes and autoimmune diseases and positive for obesity and HT (father).

The physical examination revealed the weight 95 kg (>97 percentile), height 170 cm (75-90 percentile), BMI 33.3 kg/m² (>97 percentile) [12], acanthosis nigricans on the neck and the axilla. Palpable thyroid gland with normal TSH level. Pubertal stage was Tanner 4/5. Based on clinical examination and laboratory results (impaired FPG) the diagnosis of obesity and prediabetes was made. The observation for type 2 diabetes was started and an adequate life style changes were initiated.

At her next visit 3 months later a visible metabolic improvement was noticed, she lost 10 kg. In her opinion, this achievement was a result of her compliance with a low-caloric diet and increased physical activity. However, glucose levels measured on her glucometer were abnormal (>200 mg/dl; >11.1 mmol/l). No additional signs and symptoms were present. She was referred to the Department of Pediatric Diabetes, presumed to be a new-onset type 2 diabetic patient.

Laboratory work-up: On admission to the hospital her laboratory work-up was remarkable for hyperglycemia (311 mg/dl; 17.2 mmol/l), elevated A1c (10.4%; 90 mmol/mol), and the urinalysis revealed both glucosuria (> 1,000 mg/dl) and ketonuria (40 mg/dl). Before the onset of medical therapy fasting insulin and c-peptide levels were 6.9 uU/ml and 0.62 pmol/ml, respectively. Autoantibodies IAA, GAD and IA2 were positive. Additional laboratory studies revealed TSH 7.898 uIU/ml, FT4 0.98 ng/dl. USG of thyroid gland showed a diffusely enlarged thyroid gland with a heterogeneous echogenicity. She was found to be positive for aTPO and aTG antibodies (Table 1).

Treatment and follow-up: The diagnosis of T1DM was made and a split-mixed insulin regimen (~ 0.5 U/kg/day) as well as fixed carbohydrate reduced-fat meal plan and exercise were initiated. Moreover, Hashimoto's thyroiditis was diagnosed and Thyroxine at 50 µg daily dose was added to her therapeutic regimen.

During the course of the next 4 months, patient's BMI was stable (29.4 kg/m²) after the first 4 weeks, and increased to 31.1 kg/m² after the next 4 weeks. During that period her insulin requirement has been slowly increasing (0.6 unit/kg/day), with average glucose levels of 110 - 180 mg/dl (6.1-10.0 mmol/l) and A1c- 6.9% (52 mmol/mol). At that point 500 mg metformin TID was added to her treatment. After the next 3 months she reduced BMI to 29.8, decreased insulin doses (~ 0.4 U/kg/day) and achieved acceptable metabolic control (A1c 6.3 %; 45 mmol/mol) (Table 3).

Discussion

According to the current nomenclature diabetes is generally divided into 'type 1 diabetes' and 'type 2 diabetes'. To distinguish one type from the other guidelines with useful differentiating features have been proposed [13]. But a question arises whether these clinical discriminators can be really relevant for a clinician who makes this differential diagnosis at present.

As illustrated in the cases described, distinction between T1DM and T2DM becomes blurred. From a clinical stand point, there were only two common features in our patients: obesity and adolescence as an age of the onset of the disease. All the other characteristics were different

PARAMETER	PATIENT 1	PATIENT 2	NORMAL RANGE
INSULIN [µ/ml]	5.1	6.9	5.0 - 15.0
PEPTIDE C [pmol/ml]	1.21	0.62	0.59 - 1.56
IAA [%] *	5.7	5.5	<5.5
GAD [U/ml] *	4.5	19.3	<1
IA2 [U/ml] *	4.1	45.4	<1
TSH [µIU/ml]	1.694	7.898	0.470-4.640
FT4 [ng/dl]	1.03	0.98	0.71-1.85
aTPO [U/ml]	0	709	<60
aTG [U/ml]	43	62	<60

- Three of recommended by IDF/ISPAD guidelines autoantibodies were measured in our patients
- Standardized assays were used to evaluate IAA, GAD and IA2 autoantibodies (RIA, DIASource Immunoassays S.A. for IAA and RIA, EUROIMMUN Medizinische Labordiagnostika AG for GAD and IA2 evaluation). Both GAD and IA2 assays were evaluated by DASP (2005) and showed both high sensitivity and specificity (a sensitivity of 84% and 70%, and specificity of 95% and 100%, respectively) [49-51]

Table 1: Patients' laboratory data summary.

and strongly suggested wrong initial diagnosis (Table 4). Based on the initial data, the boy received treatment as type 1 diabetic patient. On the other hand, the girl was presumed to have type 2 prediabetes and adequate treatment was initiated.

In accordance with the guidelines the presence of immune markers of beta cell disease is the most widely used criterion to confirm T1DM. However, the autoantibodies are also detected in general population of schoolchildren with the prevalence of 0.5 to 1.8% [14,15]. Moreover, they are present in children with diabetes phenotypically classified as T2DM with different studies reporting the frequencies from 30 to 75% [16-18]. However, recent data from TODAY study showed that only as many as 10% of adolescents with the typical features of T2DM upon further examination turned out to have signs of β -cell autoimmunity [19]. The question is whether it is just a presence of autoantibodies or maybe it is their titer that should be taken under consideration while differentiating the types of diabetes. All three measured autoantibodies, evaluated by standardized assays, were positive in our patients. Yet, the levels of GAD and IA2 greatly differed in both cases (Table 1). Although detection of islet autoantibodies is increasingly available to clinicians,

an unambiguous interpretation of their different titers remains to be elucidated.

Another question that arises is how one should classify an obese diabetic patient with the coexistence of both insulin resistance features and the presence of autoimmunity? Do we need any innovation in the diabetic nomenclature? Terms such as “double diabetes”, “ hybrid”, “mixed” or “type 1.5 diabetes” have recently been used to describe overweight or obese children with the combination of markers typical for both type 2 and type 1 diabetes [20-22]. Concurrently, term LADY has been introduced, describing young patients with islet antibodies and slowly progressive β -cell failure [23-28]. It is worth further research whether 1.5 diabetes is tantamount to LADY in obese adolescent and whether they have a common pathophysiological origin.

Based on present knowledge and follow-up period, we believe that our male patient presents a case that could be described as T2DM with symptoms including ketonuria at the onset of the disease, slightly positive autoantibodies and preserved insulin secretion. T2DM diagnosis would be consistent with his achievement of good metabolic control by having been compliant to diet and physical

DATE	JAN 2013 (admission to the hospital)	FEB 2013 - 1st follow-up	MAR 2013 - 2nd follow-up	JUN 2013 - 3rd follow-up
BODY WEIGHT [kg]	113	107	102.7	93.2
HEIGHT [cm]	173	173.5	174	175
BMI [kg/m ²]	37.1	35.5	33.9	30.4
GLYCEMIA [mg/dl]	347 – on admission 80-220 – after initial of treatment	97-140	70-120	70-120
A1c [%]	13.1		6.5	5.6
TREATMENT	Insulin ~0.3U/kg/d Diet and exercise	Insulin ~0.1U/kg/d Diet and exercise	Diet and exercise	Diet and exercise

Table 2: Patient's 1 therapeutic management.

DATE	SEP 2012 - 1st visit in Outpatients Clinic	DEC 2012 - 2nd visit in Outpatients Clinic	DEC 2012 (admission to the hospital)	JAN 2013 - 1st follow-up	FEB 2013 - 2nd follow-up	MAY 2013 - 3rd follow-up
BODY WEIGHT [kg]	95	85.5	85.5	85	90	86
HEIGHT [cm]	170	170	170	170	170	170
BMI [kg/m ²]	33,3	29.7	29.7	29.4	31.1	29.8
GLYCEMIA [mg/dl]	108 - 110	200 - 300	311	120 - 160	110 - 180	70-150
A1c [%]			10.4		6.9	6.3
TREATMENT	Diet and exercise	Hospital Referral	Insulin: ~0.5 U/kg/d Thyroxine 50 μ g OID Diet and exercise	Insulin: ~0.5 U/kg/d Thyroxine 50 μ g OID Diet and exercise	Insulin: ~0.6 U/kg/d Metformin 500 mg TID Thyroxine 50 μ g OID Diet and exercise	Insulin: ~0.4 U/kg/d Metformin 500 mg TID Thyroxine 50 μ g OID Diet and exercise

Table 3: Patient's 2 therapeutic management.

Characteristic	Patient 1	Patient 2
Age of onset	Pubertal period	After puberty
Clinical presentation	Rapid	Slow
Autoimmunity	Weakly positive	Positive
Ketonuria	++	+
Glycemia	High	High
Obesity	Yes	Yes
Acanthosis nigricans	No	Yes
Additional autoimmune disease	No	Yes
Diagnosis of diabetes on routine physical examination	No	Yes
T2D in family history	Yes	No
HTN in family history	Yes	Yes
Obesity in family history	No	Yes
Autoimmune disease in family history	No	No

(Highlighted features characteristic for T2DM)

This table shows how blurred the initial diagnosis of DM in such patients can be. Despite presence of obesity, rapidly developing symptoms accompanied by hyperglycemia and elevated A1C seen in our male patient suggested T1DM diagnosis. On the other hand, the girl presented the typical clinical phenotype of T2DM with features of insulin resistance (obesity, acanthosis nigricans) and slow clinical presentation, but also with high titers of islet autoantibodies

Table 4: Patients' presented characteristics.

activity recommendations. Yet, at this point of the course of the disease we cannot rule out a future development of an insulin-dependency. If such a situation occurs, he will be diagnosed as LADY characterized by the slow progression of β -cell dysfunction [29]. Such a case report was presented by Zachariah et al., who demonstrated that autoimmune diabetes can be slowly progressive even in younger patients with insulin independency period lasting for more than two years [30]. Conversely, our female patient rather seems to have T1DM, with high titers of autoantibodies and lower endogenous insulin production. Concomitantly, she was diagnosed with autoimmune thyroiditis, which coexists commonly with T1DM as a part of APS III [31]. However, she should not be classified as “classic” T1DM due to presence of obesity previous to diabetes diagnosis. T1DM in an obese child or adolescent might be called “double diabetes” [32]. According to P. Pozzilli a subject may be defined as affected by “double diabetes” in two clinical situations: when a child with T2DM has autoantibodies to beta cells or when a child with T1DM is overweight/obese, as seen in the case of our patient [33]. Moreover, our female patient exemplifies how beneficial adding metformin to therapeutic regimen may become in such cases (“double treatment” for “double diabetes”).

A meta-analysis of 9 studies (total 2658 patients) revealed an association between childhood obesity, or higher BMI, and an increased risk of subsequent type 1 diabetes showing that obesity does not exclude development of autoimmunization process and is not a protective factor against T1DM [34]. What is more, up to 21% children with a new onset T1DM were overweight or obese in the US population based study conducted by CDC [35]. The suggestion that T1DM and T2DM have a common pathophysiological origin was firstly put forward by Prof. Wilkin TJ in the ‘Accelerator Hypothesis’, describing weight gain as the missing link between type 1 and type 2 diabetes [36]. The hypothesis emphasizes the role of the body mass place in the development of both type 1 and type 2 diabetes, indicating control thereof as the potential method not only to prevent T2DM, but also to delay T1DM manifestation [37].

The ability to measure insulin resistance consistently across the phenotypic spectrum of diabetes is therefore important as it may contribute to a more accurate characterization of diabetes type. According to SEARCH study, an approach using diabetes autoantibodies and a newly developed algorithm to assess insulin sensitivity based on routine clinical measures (waist circumference, triacylglycerol and A1c) classifies >90% of youths with new-onset diabetes into one of the traditional categories. At the same time, it identifies a group of youths who would benefit from further testing to clarify the etiology of diabetes [38,39].

Whereas detailed understanding of the pathogenesis of the types and subtypes of diabetes remains to be elucidated, it is apparent that there is a genetic predisposition on which environmental triggers are superimposed. HLA-typing may lead not only to better comprehension of the pathological background of emerging subtypes of diabetes, but also to avoid misclassification of diabetic patients and to evaluate the risk of the disease in the family members [40]. Although advances in genotyping technology have been witnessed lately, genetic testing for T1DM and T2DM still remains of little value in clinical practice, mainly in pediatric population [41,42].

To conclude, the dilemma of categorizing the type of diabetes in children and adolescents was thoroughly presented. However, not to discount the importance of classifying diabetes in an obese child, it is the therapeutic approach to such a complex patient that a physician should mainly focus on. Would it be helpful in proposing a better treatment

for a patient once we sort out what subtype of diabetes he or she has? It is worth mentioning that since the course of T2DM relies on the presence of islet autoantibodies, the necessity of marking them seems to be equally crucial in further therapeutic decisions [43]. Nevertheless, it seems reasonable to treat a patient based on his or her actual needs: insulin deficiency will always require treatment with insulin, while insulin resistance gives us a choice of a few therapeutic approaches. Yet, therapeutic options for type 2 diabetic children and adolescents are limited [44]. While we follow guidelines treating patients with classic types of diabetes, it is still unclear how to approach non-classic picture of the disease, particularly in the long-term treatment. It is worth mentioning that diabetic patients with preserved beta cells function and concomitant high levels of autoantibodies may benefit from early insulin treatment [45]. On the other hand, there is some evidence of a significant effect of metformin used in type 1 diabetic patients, especially those with poor control of the disease and coexisting obesity [46-48]. However, regardless of the type of diabetes we have to deal with and the therapeutic approach we choose, still the main goal is to prevent chronic complications by achieving a good metabolic control of the disease [49-51].

Conclusions

- In the face of increasing prevalence of obesity worldwide, the diagnosis of diabetes has become a new challenge for physicians.
- At the onset of diabetes it seems important to put an impact on an adequate treatment, leaving the differential diagnosis to the subtypes of the disease to the follow-up period.
- Based on present knowledge, pathophysiology of new subtypes of diabetes is still unclear, making it often impossible to classify the patient properly.
- Recently, since new phenotypes and courses of diabetes have been observed, common standpoint in the classification of diabetes might be proposed.

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