Acta Biomed 2021; Vol. 92, N. 5: e2021511 DOI: 10.23750/abm.v92i5.11598

Original Article

Clinical and metabolic characteristics of children with hybrid diabetes mellitus (HD) compared to children with type 2 diabetes mellitus (T2DM): A preliminary comparative study

Noor Hamed [1], Ashraf Soliman [1], Vincenzo De Sanctis [2], Fawzia Alyafei [1], Nada Alaaraj [1], Shayma Ahmed[1], Ahmed Elawwa [1,3,4]

[1] Department of Pediatric Endocrinology, Hamad General Hospital, Doha, Qatar; [2] Pediatric and Adolescent Outpatient Clinic, Quisisana Hospital, Ferrara, Italy; [3] Department of Pediatric Endocrinology, Sidra Medicine, Doha, Qatar; [4] Department of Pediatrics, Alexandria University, College of Medicine, Alexandria, Egypt.

Abstract. *Background:* The term double diabetes or "Hybrid Diabetes (HD)" describes diabetes with combined features of type 1 and type 2 diabetes (T2DM). Typically, HD is characterized by insulin resistance, obesity, and the presence of markers of β-cell autoimmunity. Differentiating HD from other forms of diabetes is important for a better understanding of the disease process and course, as well as for an appropriate management plan to prevent future complications. *Patients and Methods:* We report the clinical and biochemical characteristics of 7 children with HD and the course of their disease including the response to treatment. The data were compared to 59 children with a diagnosis of T2DM. Variables examined included age, height, weight, body mass index (BMI), triglycerides (Tg), high-density lipoprotein (HDL), and blood pressure. The Weiss criteria were used to diagnose metabolic syndrome (MetS). The atherogenic index of plasma (AIP) was calculated from the standard lipid profile. Four autoantibodies against pancreatic β-cell were measured in all patients. *Results:* Significant clinical and biochemical differences were detected among children with HD versus T2DM. The mean BMI of children with T2DM was significantly higher than for the HD group. At presentation, the mean C peptide level was significantly lower in HD versus T2DM group and 28% presented with diabetic ketoacidosis (DKA). The percentage of those with full criteria of MetS was significantly higher in T2DM versus HD group as well as the percentage of children with high atherogenic index. After a mean duration of 2.3 months from diagnosis, 4/7 of HD patients stopped insulin therapy and 3 patients had a marked reduction in the insulin requirement. During the follow-up (after 15 ±5 months), 5/7 HD patients required an increase in their insulin dose, one was controlled on a markedly low dose of basal insulin and the last patient did not require any insulin therapy for 40 months. *Conclusion:* Classifying a clinical condition is very important in disease diagnosis and treatment as it can guide clinicians to translate scientific understanding to clinical practice. Appropriate assessment of HD is necessary for early and correct diagnosis. Increasing awareness of HD among the general population and primary care practitioners is necessary for successfully and properly treating this complex disease. (www.actabiomedica.it)

Keywords: Hybrid diabetes (HD), type 2 diabetes mellitus, metabolic syndrome (MetS), follow-up, treatment, children.

Introduction

The term double diabetes or "Hybrid Diabetes (HD)" is a new term that emerged in the last few years to describe diabetes with combined features of type 1 (T1DM) and type 2 diabetes (T2DM). It is characterized by the occurrence of hyperglycemia in children and young adolescents with the combination of markers typical of both T1DM and T2DM. Typically, HD is characterized by insulin resistance, obesity, and the presence of markers of β-cell autoimmunity. Family history for T2DM and T1DM may be also present (1).

The 'accelerator hypothesis' argues that T1DM and T2DM are one and the same disorder, but distinguishable by the measure and tempo of three accelerators, one being intrinsic and two being acquired (2). The accelerators include β-cell death, insulin resistance, caused by weight gain, visceral fat and sedentary lifestyle, and β-cell autoimmunity (immune damage), driven by genetic factors (2,3).

A large epidemiological survey has shown that a total of 25.5% of patients suffering from T1DM additionally present a metabolic syndrome (4,5). In another study, including 200 patients with youth onset diabetes, 7% were categorized as HD (6).

Unlike T1DM and T2DM, there is no consensus on the therapeutic modalities for HD (7).

Differentiating HD from other forms of diabetes is important for a better knowledge of disease and course process, and for appropriate management in order to prevent future complications (8-10).

The clinical characteristics of children with HD have not fully described. The main aim of the present study is to report the clinical and biochemical data of children with HD and to compare their characteristics to those with T2DM.

Patients and Methods

The clinical and biochemical characteristics of 7 children (10.8 ± 0.98 years) with HD were compared to 59 children diagnosed as T2DM (age range: 7 -18 years) at the Department of Pediatric Endocrinology, Hamad General Hospital, Doha (Qatar).

Variables examined included: age, height, weight, body mass index (BMI), triglycerides (Tg), high-density lipoprotein (HDL), and systolic and diastolic blood pressure (SBP and DBP). The diagnosis of metabolic syndrome (MetS), based on Weiss criteria, included the following five criteria: (a) an elevated TG level >95th percentile (age, sex and race specific), (b) a reduced HDL-C level < 5th percentile(age, sex and race specific) , (c) a raised BP > 95th percentile (age, sex and height specific), (d) an impaired glucose tolerance(ADA criteria), and (e) BMI z score >2(age, sex specific) (11). The atherogenic index of plasma (AIP) was calculated from the standard lipid profile. Hypertension was defined as SBP or DBP in the 95th percentile or greater for sex, age, and height.

Four autoantibodies against pancreatic β-cell were measured in all patients. These included islet cell antibodies (ICA), antibodies to glutamic acid decarboxylase (GAD-65), insulin autoantibodies (IAA), and protein tyrosine phosphatase (IA-2A) (12). Pancreatic autoimmunity was defined as at least one of four autoantibody-positive results.

Results

At presentation, all children with HD were obese, with a mean BMI standard deviation score (SDS) of 2.73 ± 0.58. 5/7 had acanthosis nigricans (AN), 6/7 had a family history of DM (T1DM: 3 patients, T2DM:1 patient, and gestational diabetes: 1 patient). A greater proportion of patients was female (Table 1).

Two patients resulted positive for 2 pancreatic β-cell autoantibodies, 3 patients for 3 autoantibodies, and two patients for all autoantibodies. The most prevalent autoantibody was the anti-GAD-65 (all patients). The mean glycated hemoglobin (HbA1c) at diagnosis was 10.6 ± 2.1%.

At diagnosis, 4/7 patients presented with the classical symptoms of polyuria, polydipsia, and weight loss along with hyperglycemia. Two patients had moderate/severe diabetic ketoacidosis (DKA) and one patient presented with ketosis and polyuria. In all patients, insulin treatment was started at diagnosis associated with lifestyle modification and 5/7 patients received metformin in the first week after diagnosis.

Table 1. Clinical characteristics, at presentation, in 7 children with hybrid diabetes (HD).

Case (no)	Age (yr)	BMI SDS	Presence of acanthosis nigricans	Family history of DM	At presentation	C-peptide (nmol/L)	Numbers of β-cell antibodies (no.)	Hb A1c %
1	12	2.37	no	Type 1 DM	Hyperglycemia	1.24	2	10.6
2	10	2.5	yes	GDM	DKA		3	
3	11.2	3.56	no	Type 2 DM	Hyperglycemia	0.92	4	12.9
4	11	2.12	yes	Type 1 DM	Hyperglycemia	3.94	3	9.7
5	9.3	2.31	yes	None	Hyperglycemia		3	8.7
6	10.9	3.51	yes	Type 2 DM	DKA	0.41	3	8.5
7	10.8	2.77	yes	Type 2 DM	Hyperglycemia + mild ketosis	0.59	2	13.4

Abbreviations and reference value = **BMI:** body mass index; **GDM**: gestational diabetes mellitus; **DM:** diabetes mellitus; **DKA:** diabetic ketoacidosis; **C-peptide** normal fasting range values: 0.26-0.62 nmol/L.

After a mean duration of 2.36 months from diagnosis, 4/7 patients did not require insulin treatment, and the other 3 patients had a marked reduction of insulin dose requirement (less than 0.2 unit/kg/day) to attain good glycemic control. After 15 ± 5 months, insulin treatment was restarted or increased in 5 patients, one was still controlled with a markedly low dose of basal insulin (0.06 unit/kg/day) and the last patient did not require any insulin therapy for the subsequent 40 months.

In the first 2 months, after diagnosis, the mean BMI SDS decreased from.2.8 ± 0.45 to 2.39 ± 0.5, with a mean delta change of -0.34SDS. The mean HbA1c also decreased, two months after diagnosis, to 6.3± 0.7% (Table 2).

The comparison between children with HD versus those with T2DM is presented in table 3. The age at presentation did not differ between the 2 groups. The mean BMI SDS of T2DM was significantly higher compared to the HD group (p= < 0.04). None of the T2DM patients presented with DKA, while 28% of children with HD presented with DKA. No significant difference among the two groups was found regarding family history of DM, presence of AN, polyuria, and polydipsia or HbA1c concentration. The mean C peptide level at presentation was significantly higher in the T2DM versus HD group (p= 0.01). The percentage of patients with full criteria of MetS was significantly higher in the T2DM versus HD group and the percentage of children with high atherogenic index was significantly higher in the T2DM versus HD (Table 3).

Table 2. Follow up data in 7 children with hybrid diabetes (HD) showing their prolonged honeymoon period and their requirements of insulin and metformin during this period.

Case no	Duration before stopping insulin or significant reduction of dose	First BMI SD after therapy	Delta BMI SD	HbA1c % after therapy	Duration off insulin/or on basal only (months) (honeymoon?)	Insulin required kg/day during honeymoon	Insulin upgrade needed after honeymoon	Metformin dose mg/day
1	8 months	1.82	-0.55	5.5	11	0.06	No	500
2	2 weeks	2.18	-0.32	6	10	0	Yes	2000
3	2 months	2.93	-0.63	6.2	12	0	Yes	1500
4	4 months	2.11	-0.01	6.4	8	0.13	Yes	500
5	2 weeks	1.96	-0.35	6.3	15	no	Yes	1000
6	2weeks	3.25	-0.26	7.8	9	0.2	yes	1500
7	1 month	2.48	-0.27	6	40	0	No	1500

Table 3. Comparison between 59 children with type 2 diabetes mellitus (T2DM) versus 7 children with hybrid diabetes (HD).

	Hybrid Diabetes	Type 2 diabetes mellitus	p value
Number	7	59	--
Age at presentation (yr)	10.8	11.28	0.50
Male: Female ratio	0.71	0.37	<0.0001
BMI SDS	2.8	4.5	0.04
Acanthosis nigricans (%)	71	90	0.16
Family history of diabetes mellitus (%)	85.7	87	0.29
Polyuria/polydipsia (%)	57.1	78	0.22
Ketosis no acidosis (%)	14.2	22	0.64
Diabetic ketoacidosis (DKA;%)	28.6%	0%	< 0.00001
C-peptide level (nmol/L)	1.42	3.88	0.01
Pancreatic β-cell antibodies positivity (%)	100	0	<0.0001
HbA1c at diagnosis (%)	10.6	10.0	0.61
HbA1c after 15 ± 5 months (%)	9.8	8.9	0.3536
High low-density lipoprotein (LDL) (%)	28.5	51.5	< 0.00001
Hypertension (%)	28.5	33.3	0.8063
Metabolic syndrome (%)	42.8	80	<0.0001

Discussion

The current classification of DM is primarily based on etiology and includes T1DM, T2DM, gestational diabetes, and other types of DM. Traditionally, T1DM is a condition that affects lean children or adolescents, and young adults. Clinical and pathophysiological characteristics of T1DM and T2DM in the same patient have been designated as HD. Increasing clinical evidence is emerging that highlights marked overlap between these two diabetic conditions (13). Therefore, the current classification of diabetes into two distinct diseases likely does not reflect the true nature of most cases (13,14).

"Hybrid Diabetes" is a new term that has been used just in the last few years to describe diabetes with combined features of type 1 and type 2 diabetes at presentation. This newly a recognized subtype of diabetes has special characteristics that differentiate it from other types of diabetes. HD is not a simple, single clinical entity, but comprises a rather broad, mixed range of complex pathophysiological disease features, including impaired immunity, insulin resistance, environmental, and lifestyle (3, 5-7).

A number of relevant findings emerged from our study: (a) children with HD were less obese, and presented a higher risk to develop DKA compared to T2DM patients; (b) children with HD (positive autoantibodies) had lower C peptide level compared to those with T2DM (negative autoantibodies); (c) the prevalence of MetS in children with HD was significantly lower compared to those with T2DM, and (d) the combination of lifestyle modification, insulin and/or metformin treatments were successful to attain good metabolic control.

Although our preliminary results denoted early improvements of insulin resistance and/or endogenous insulin secretion, a question still remains open "does this improvement represent a long honeymoon period in a patient with relative insulin deficiency or this is due to the reversal of glucotoxicity on β-cell function during insulin plus metformin treatment"?

As our patient, Braham et al. (15) described a group of 92 HD patients who presented with hyperglycemia, high BMI, and high fasting C peptide. Their age at diagnosis (15.1 ± 6.4 years) was older than our patients. A total of 41% of their study population presented with DKA and 61% presented a positive family history of DM. 64% of them were overweight or obese. Moreover, 92% of their patients were started on insulin therapy at the time of diagnosis. During the follow-up (mean: 3 years), only 32% required insulin,

and 78% were on treatment with metformin alone or associated with insulin.

For decades it has been reported that relieving hyperglycemia can itself improve insulin secretion and restore metabolic control, at least temporarily. In addition, targeted anti-inflammatory therapy using an IL-1β antagonist, and GLP-1 receptor agonists have demonstrated that β-cell dysfunction can be reversed temporarily. However, the durability of these effects following therapy withdrawal remains challenging (16-18).

Most of our HD patients, after the first 15 ± 5 months of treatment, required re-initiation or increasing insulin doses despite having lower or similar BMI SDS compared to their values at diagnosis, suggesting a deterioration of endogenous insulin secretion. Interestingly, all our patients with HD had 2 or more β-cells autoantibody-positive at presentation with C-peptide ranging between 0.6 to 3.94 nmol/L (mean = 1.42 nmol/L; normal range values: 0.26-0.62 nmol/L).

Pancreatic islet autoantibodies are thought to indicate a progressive autoimmune disease in the β-cells associated with a gradual decrease in insulin secretion. In autoimmune diabetes, Torn et al. (19) found that a low C-peptide level (below 0.25 nmol/L) and a high GAD-65 at diagnosis were risk factors for a decrease in β -cell function. The levels of other autoantibodies (ICA or IA-2A or IAA) or factors such as age, BMI, or gender were of no prognostic importance for the course of β-cells function.

Several pieces of evidence indicate that individuals who display features of HD are at higher risk of developing future diabetes complications, independently of average glucose control, measured by HbA1c concentrations (4,20,21). In our study, the prevalence of MetS was significantly lower compared to those with T2DM. Moreover, our patients had a significantly lower occurrence of AIP, which is one of the strongest markers in predicting the cardiovascular disease risk (CVD) (22), and a lower occurrence of increased LDL compared to those with T2DM. Nevertheless, attention should be paid to the management of these patients and long-lasting follow-up is needed before definitive conclusions.

In conclusion, HD is a distinct subtype of DM characterized by the co-existence of the etiologic processes of autoimmunity and the peripheral defects in insulin signaling. Its recognition might facilitate more tailored approaches to treatment, clinical care, and follow-up, as well as help minimize the development of chronic complications. Classifying a clinical condition is very important in disease diagnosis and treatment as it can guide clinicians to translate scientific understanding to clinical practice.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Mottalib A, Kasetty M, Mar JY, Elseaidy T, Ashrafzadeh S, Hamdy O. Weight management in patients with Type 1 diabetes and obesity. Cur Diab Rep 2017; 17:92.
2. Knerr I, Wolf J, Reinehr T, et al ; DPV Scientific Initiative of Germany and Austria. The 'accelerator hypothesis': relationship between weight, height, body mass index and age at diagnosis in a large cohort of 9,248 German and Austrian children with type 1 diabetes mellitus. Diabetologia 2005; 48:2501-4.
3. Wilkin TJ. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type I as well as type II diabetes. Int J Obes (Lond) 2009; 33:716–26.
4. Merger S R, Kerner W, Stadler M, et al; DPV Initiative; German BMBF Competence Network Diabetes mellitus. Prevalence and comorbidities of double diabetes. Diabetes Res Clin Pract 2016; 119:48-56.
5. Weiss R, Bremer AA, Lustig RH. What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci 2013; 1281:123-40.
6. Mishra B K, Shukla P, Aslam M, Siddiqui AA, Madhu SV. Prevalence of double diabetes in youth onset diabetes patients from east Delhi and neighboring NCR region. Diabetes Metab Syndr 2018;12: 839–42.
7. Kaufman F. 'Double diabetes' in young people and how to treat it. Diabetes Voice 2006; 51:19-22
8. Pozzilli P, Guglielmi C, Caprio S, Buzzetti R. Obesity, autoimmunity, and double diabetes in youth. Diabetes Care 2011;34 (Suppl 2): S166-70.
9. Pozzilli P, Guglielmi C. Double Diabetes -A mixture of Type 1 and Type 2 Diabetes in youth. Endocr Dev 2009; 14: 151–66.
10. Khawandanah J. Double or hybrid diabetes: A systematic review on disease prevalence, characteristics and risk factors. Nutr Diabetes 2019; 9:33.
11. Weiss R, Bremer AA, Lustig RH. What is metabolic syndrome, and why are children getting it? Ann N Y Acad Sci 2013; 1281:123-40.

12. Sørgjerd EP. Type 1 Diabetes-related Autoantibodies in Different Forms of Diabetes. Curr Diabetes Rev 2019; 15:199-204.
13. Purushothaman R, Ramchandani N, Kazachkova I, Ten S. Prevalence and clinical features of type 1.5 diabetes mellitus in children. J Pediatr Endocrinol Metab 2007; 20:981-7.
14. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014;383: 69-82.
15. Braham R, Alzaid A, Robert AA, et al. Double diabetes in Saudi Arabia: A new entity or an underestimated condition. World J Diabetes 2016; 7:621-6.
16. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. Lancet 2008; 371:1753–60.
17. Larsen CM, Faulenbach M, Vaag A, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med 2007; 356:1517–26.
18. Bunck MC, Diamant M, Cornér A, et al. One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care 2009; 32:762–8.
19. Törn C, Landin-Olsson M, Lernmark A, et al. Prognostic factors for the course of beta cell function in autoimmune diabetes. J Clin Endocrinol Metab 2000; 85:4619-23.
20. Kietsiriroje N, Pearson S, Campbell M, Ariëns RAS, Ajjan RA. Double diabetes: A distinct high-risk group? Diabetes Obes Metab 2019; 21:2609-18.
21. Khawandanah J. Double or hybrid diabetes: A systematic review on disease prevalence, characteristics, and risk factors. Nutr. Diabetes 2019;9(1):33.
22. Bo MS, Cheah WL, Lwin S, Moe Nwe T, Win TT, Aung M. Understanding the Relationship between Atherogenic Index of Plasma and Cardiovascular Disease Risk Factors among Staff of an University in Malaysia. J Nutr Metab 2018; 2018:7027624.

Correspondence:
Received: 25 March 2021
Accepted: 9 April 2021
Vincenzo de Sanctis, MD
Pediatric and Adolescent Outpatient Clinic
Quisisana Hospital
44121 Ferrara, Italy
E-mail: vdesanctis@libero.it