https://doi.org/10.46389/rjd-2021-1027
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2021; volume 28, issue 2, pages 170-177

Original Research

Pitfalls in establishing type of diabetes and optimal therapy: clinical cases series

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Received: 14 May 2021 / Accepted: 10 June 2021

Abstract

Type 1 diabetes is an autoimmune disease characterized by absolute endogenous insulin deficiency. We report three clinical cases which highlight the particularities of diagnosis and evolution of patients with type 1 diabetes. These three cases have been diagnosed in different circumstances. The first case with symptoms of hyperglycemia and inaugural diabetic ketoacidosis, without detecting a precipitating factor; the second case accidentally diagnosed, in the absence of hyperglycemia symptoms; and the last case in the context of symptoms of hyperglycemia and ketosis precipitated by a respiratory infection. The cases are characterized by the presence of autoimmunity markers (anti-GAD positive antibodies) and C-peptide within normal range. In dynamics, with the initiation of insulin therapy and the remission of glucotoxicity, the insulin requirement decreased progressively, in all patients therapeutic regimen being represented by a low dose of basal insulin, in the conditions of a C-peptide still within normal limits at 4 years (first case), 1 year (second case), respectively 2 years (third case) from the diagnosis and without significant glycemic variability registered on the continuous glycemic monitoring system. In the third case, there is a lack of regression of insulin requirements after remission of SARS COV-2 infection, and in the second case, the maintenance of prandial insulin secretion sufficient to induce hypoglycemia after administration of a minimal dose of prandial insulin, but insufficient to control post-prandial glycemia in the conditions of omitting the administration of prandial insulin. In each of the cases previously presented we highlight the existing pitfalls in establishing the diagnosis and especially the challenges in choosing the optimal therapy in patients with type 1 diabetes, as the evolution can sometimes be atypical.

Keywords: continuous glucose monitoring system, glycemic variability, insulin secretion, time in range, type 1 diabetes

Background and Aims

Type 1 diabetes mellitus (DM) is considered an autoimmune disease with multifactorial etiology, characterized by destruction of pancreatic beta cells, reaching in time the absolute endogenous insulin deficiency [1]. The rate of beta cell destruction is quite variable, being aggressive in some individuals (mainly infants and children) and slow in others (mainly adults) [2].

Autoimmune markers characteristic to type 1 DM includes: glutamic acid decarboxylase (GAD) antibodies, tyrosine phosphatase antibodies (IA2A), insulin autoantibodies (IAA), islet cell antibodies (ICA) and the zinc transporter antibodies (anti-ZnT8 antibody) [1, 3].

Patients with type 1 diabetes are also at risk to develop other autoimmune disorders such as Hashimoto thyroiditis, Graves disease, celiac disease, Addison disease, vitiligo, autoimmune hepatitis, myasthenia gravis or pernicious anemia.

At first glance, type 1 diabetes pathophysiology and management might seem

straightforward, however, the more that is learnt about the disease, the less it seems is truly known. What once seemed like a single autoimmune disorder, originating in T cell-mediated β-cell destruction, is now recognized to result from a complex interplay between environmental factors and microbiome, genome, metabolism and immune system that vary between individual cases [4].

The current cases series presentation highlights the pitfalls in establishing the diagnosis, as well as the challenges of choosing the optimal therapy for patients with diabetes. Thus, a series of three clinical cases are presented in which the particularities of diagnosis and evolution of patients with diabetes are highlighted.

Materials and Methods

Case report no 1

On the first case, we present a 19-year-old patient, without a hereditary history of diabetes, obesity or cardiovascular diseases, diagnosed with type 1 diabetes mellitus 4 years ago, in the context of the signs and symptoms of hyperglycemia (polyuria, polydipsia and weight loss of approximately 12 kg within 1 year) and inaugural diabetic ketoacidosis without detecting a precipitating factor.

Physical exam at diagnosis revealed underweight (height 170 cm, weight 52 kg, body mass index [BMI] 17.99 kg/m^2) and waist 68 cm.

Laboratory data at diagnosis revealed fasting plasma glucose 362 mg/dL, HbA_{1c} 13.01%, urinary ketone bodies 150 mg/dL (maximum laboratory detection), anti-GAD antibodies 135 IE/mL (normal value: 1.1–4.4 ng/mL). Screening for autoimmune thyroiditis was performed by dosing anti-thyroglobulin and anti-thyroperoxidase antibodies, the screening being negative. Fundoscopy did not reveal lesions of diabetic retinopathy. The rest of the explorations that could have highlighted the presence of a precipitating factor of ketoacidosis (EKG, kidney and liver function, urine culture, chest X-ray, ultrasound of abdomen, pelvis and thyroid) were within normal limits.

At diagnosis, basal bolus insulin therapy with Novo-Rapid (NR) insulin and Lantus insulin was initiated, with dose titration according to glycemic profile. The recommended insulin therapy regimen at hospital discharge was 6 IU NR-6 IU NR-5 IU NR-9 IU Lantus, the total daily insulin dose being 0.5 IU/kg. It was recommended glycemic self-monitoring and titration of insulin doses based on glycemic profile.

The patient was re-evaluated clinically and metabolically within 8 months of diagnosis, when a weight gain of 9 kg was detected, possibly secondary to frequent episodes of hypoglycemia supported by a significant reduction in HbA_{1c} (5.1%) and by reporting episodes of imperious hunger, remitted after ingestion of carbohydrates, the patient omitting the determination of blood glucose before the carbohydrates intake.

The potential explanation for hypoglycemic episodes is the lack of regressive titration of insulin doses in the context of the onset of transient remission of diabetes associated with decreased glucotoxicity.

Continuous glycemic monitoring was initiated and based on the evolution of the glycemic profile, regressive titration of insulin doses was performed, establishing the following therapeutic regimen: 4 IU NR-4 IU NR-4 IU NR-4 IU Lantus, the total daily insulin dose being 0.25 IU/kg.

On this therapeutic regimen, on the records of the continuous glycemic monitoring system, no important glycemic variables were highlighted, the percentage of time with glycemic values in target (70–140 mg/dL) being 97%, the coefficient of variation (CV) was 16.6%, no glycemic values lower than 70 mg/dL were registered, the percentage of time spent with glycemic values above the target (140 mg/dL) was only 3%, the maximum glycemic value being 162 mg/dL, without significant post-prandial glycemic excursions and without inter-day glycemic variability (Figure 1).

This insulin requirement was maintained relatively constant for a period of about 2 years, with no changes in body weight, and the HbA_{1c} value ranged between 5.1% and 5.8%.

The evolution of glycemic profiles imposed the gradual decrease of insulin doses, therefore at 4 years after diagnosis, the

	Tue 03.09	Wed 04.09	Thu 05.09	Fri 06.09	Sat 07.09	Sun 08.09	Mon 09.09	Average / Total
# Sensor Values	134	288	288	288	288	288	107	1.681
Highest	144	161	149	130	162	132	142	162
Lowest	85	72	88	83	81	73	74	72
Average	112	101	114	99	105	94	86	102
Standard Dev.	16	16	16	10	16	12	18	17
MAD %	13,7	18,2	24,0	5,9	9,0	3,5	7,1	13,7

Excursion Summary (mg/dL/day)

	Tue 03.09	Wed 04.09	Thu 05.09	Fri 06.09	Sat 07.09	Sun 08.09	Mon 09.09	Average / Total
# Excursions	1	1	1	0	2	0	1	6
# High Excursions	1	1	1	0	2	0	1	6
# Low Excursions	0	0	0	0	0	0	0	0
AUC Above Limit	0,1	0,5	0,5	0,0	0,6	0,0	0,0	0,3
AUC Below Limit	0,0	0,0	0,0	0,0	0,0	0,0	0,0	0,0

Duration Distribution (hh:mm)

Above 140	0:30	4%	0:50	3%	1:50	8%	0:00	0%	1:25	6%	0:00	0%	0:10	2%		4:45	3%
Within (70 - 140)	10:40	96%	23:10	97%	22:10	92%	24:00	100%	22:35	94%	24:00	100%	8:45	98%		135:20	97%
Below 70	0:00	0%	0:00	0%	0:00	0%	0:00	0%	0:00	0%	0:00	0%	0:00	0%		0:00	0%

Figure 1: Glycemic profile, pattern snapshot and excursion summary assessed by continuous glucose monitoring system.

https://doi.org/10.46389/rjd-2021-1027

administration of prandial insulin was stopped, the patient's therapeutic regimen being represented only by basal insulin (3UI Lantus) administered in the morning.

Biological assessment after 6 months period with basal insulin therapy alone showed a normal C-peptide value – 1.9 ng/mL (normal value: 1.1–4.4 ng/mL), HbA_{1c} – 6%, and glycemic values in the established interprandial and post-prandial glycemic targets.

Case report no 2

In the second case, we present a 31-year-old patient, without a hereditary history of diabetes, obesity or cardiovascular disease, diagnosed a year ago with type 1 diabetes, by coincidence, in the absence of signs and symptoms of hyperglycemia, during routine investigations that showed fasting blood glucose 130 mg/dL and 6.4% HbA_{1c}.

The clinical evaluation revealed a normal weight (height 173 cm, weight 61 kg, BMI 20.3 kg/m^2, maximum BMI 23.7 kg/m^2) and waist 82 cm.

Although at that time the classical criteria for diabetes diagnosis were not met, considering the young age of the patient, biological investigations were continued with the dosing of anti-GAD antibodies – >256 IE/mL (normal value < 10 IE/mL), C-peptide – 0.59 ng/mL (normal value: 0.8–3.8 ng/mL) and urinary ketone bodies are absent.

The fundus examination of eye was performed and did not show diabetic retinopathy. Basal-bolus insulin therapy was initiated with Fiasp and Tresiba insulin in doses that have been titrated according to the evolution of the glycemic profile up to a requirement of 3 IU Fi- 3 IU Fi- 3 IU Fi- 6 IU Tresiba (0.24 IU/kg).

After 1 year diagnosis, the patient presents for significant glycemic variability with frequent episodes of symptomatic severe hypoglycemia (glycemia 14 mg/dL), occurring post-prandial, even on the minimum dose of prandial insulin (1UI Fiasp administered preprandial for a quantity of 60–70 g carbohydrates), but with glycemic values that exceed the post-prandial targets in the absence of prandial insulin administration.

Also, glycemic self-monitoring indicated hyperglycemia at one hour post-prandial (440 mg/dL) justified by the omission of preprandial Fiasp administration and a high intake of concentrated sweets and fast food, hyperglycemia which suggested the need to administer 4 IU of Fiasp, administration that caused a sudden and significant drop in blood glucose level, reaching the value of 50 mg/dL within 45 minutes, accompanied by specific symptoms of hypoglycemia and difficult to correct by administration of sugar and carbohydrates.

Evaluation of insulin secretion indicated a low value of fasting C-peptide – 0.9 ng/mL (normal value: 1.1–4.4 ng/mL) and a normal value of C-peptide at 1 hour after a mixed lunch – 1, 39 ng/mL (normal value: 1.1–4.4 ng/mL).

Given both the evolution of the glycemic profile and the value of post-prandial C-peptide, it was recommended to stop the administration of prandial insulin, the administration of basal insulin (6 IU Tresiba) in the morning and the combination of alpha-glucosidase inhibitors (Glucobay 50 mg) before main meals. The favorable evolution of the glycemic profile was observed without detecting episodes of hypoglycemia and without important post-prandial glycemic excursions.

Case report no 3

In the last case, we present a 17-year-old patient with a hereditary history of type 2 diabetes on the paternal line (grandmother, great-grandmother), who was diagnosed 2.5 years ago with type 1 diabetes in the context of the signs and symptoms of hyperglycemia (polyuria, polydipsia and weight loss of 8 kg) with 2 months duration and ketosis which had as a precipitating factor an upper respiratory tract infection.

Clinical examination at diagnosis revealed normal weight (height 181 cm, weight 72 kg, BMI 21.98 kg/m^2) and a normal waist (82 cm).

Para-clinical examinations at diagnosis revealed venous blood glucose 267 mg/dL, HbA_{1c} 10.5%, urinary ketone bodies 150 mg/dL (maximum laboratory detection), C-peptide 2.73 ng/mL (normal value: 1.1–4.4 ng/mL), C-peptide value should be interpreted in the context of glucotoxicity, anti-GAD antibodies 56 IE/mL

Figure 2: Glycemic profile and time in range overview (90 days period).

(normal value: <10 IE/mL) and anti-IA2 antibodies >4000 IE/mL (normal value: <10 IE/mL), the rest of the biological explorations being within normal limits.

Screening was performed for autoimmune thyroiditis by dosing anti-thyroglobulin and anti-thyroperoxidase antibodies and for celiac disease by measuring IgA, anti-gliadin and anti-endomysium tissue anti-transglutaminase antibodies, all antibodies being negative. Also, the diabetic retinopathy was excluded by performing the fundus examination.

At diagnosis, basal bolus insulin therapy was initiated with Novo-Rapid and Lantus insulin, in doses that were titrated based on the evolution of the glycemic profile up to a requirement of 12 IU NR-10 IU NR-8 IU NR-18 IU Lantus, the total daily insulin dose being 0.66 IU/kg.

In evolution, with the remission of glucotoxicity, insulin requirements decreased significantly, the administration of prandial insulin was stopped, the patient administering only basal insulin (4 IU Lantus) in the morning, C-peptide value remaining within normal limits (3.06 ng/mL at 5 months after diagnosis, respectively 1.34 ng/mL at 1 year after diagnosis, dosed at an HbA_{1c} value of 6.08% and 5.2%, respectively) (Figure 2).

This insulin requirement has remained relatively constant over approximately 2 years of evolution, increasing significantly during SARS COV-2 infection (January 2021) and remaining high after the remission of acute infectious phenomena, the therapeutic regimen being currently represented by basal insulin in a dose of 14 IU Lantus, to which is associated prandial insulin (1 IU for 10 g carbohydrates), under the

https://doi.org/10.46389/rjd-2021-1027

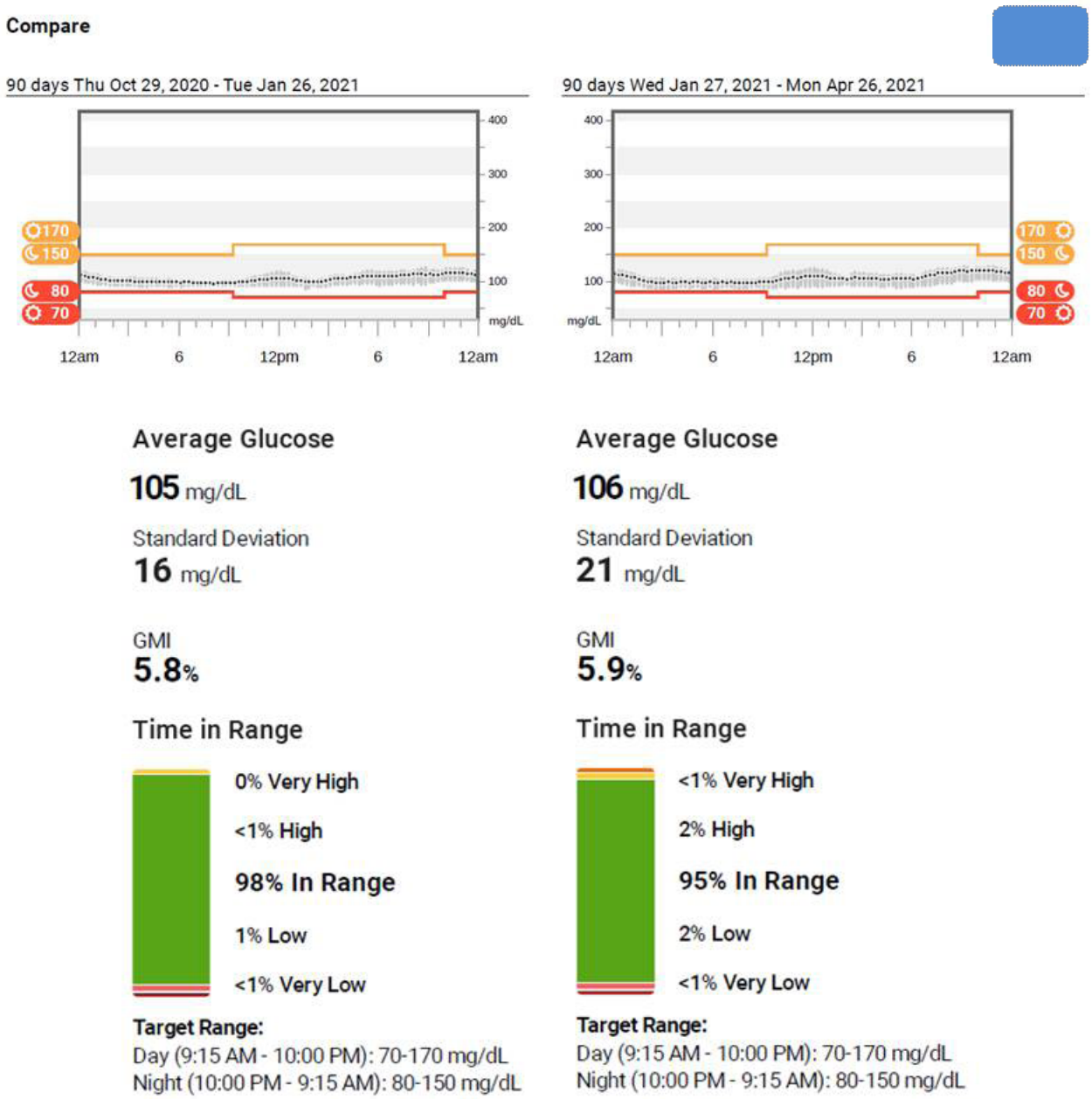

Figure 3: Glycemic variability and time in range before (left side) and after (right side) SARS COV-2 infection (January 2021).

conditions of a C-peptide of 1.27 ng/mL (normal value: 0.8–3.8 ng/mL) and a HbA_{1c} of 5.2%, without highlighting the important glycemic variability on the records of the continuous blood glucose monitoring system (Figure 3).

Discussions

Peculiarities of diagnosis and treatment of the presented cases

The peculiarity of the first case is represented by the slow and insignificant decline of insulin secretion indicated by the value of C-peptide and the very low insulin requirement with maintaining an optimal glycemic control at 4 years from diagnosis, in the context of the patient's young age, identifying markers of autoimmunity. And the clinical features of the diabetes onset that would have suggested the rapid and permanent onset of insulinopenia by autoimmune destruction of pancreatic beta cells.

The peculiarity of the second case is the maintenance of prandial insulin secretion level at the lower limit of the normal range, which explains the occurrence of hypoglycemia after

administration of a minimum dose of prandial insulin and hyperglycemia in conditions of prandial insulin omission, associated with a low level of basal insulin secretion. Administration of alpha-glucosidase inhibitors allowed the correction of post-prandial blood glucose by reducing the intestinal absorption of monosaccharides without inducing hypoglycemia. Given that the current and maximum BMI was not higher than 25 kg/m^2, we did not opt for other therapeutic options targeting post-prandial blood glucose (inhibitors of sodium glucose transporter 2 – SGLT2).

The peculiarity of the third case is represented by the slow increase of insulin requirements in a young patient with a cluster of markers of autoimmunity, an evolution that can be explained by maintaining an efficient level of insulin secretion indicated by C-peptide values, clinical and biological characteristics presented at the time of diabetes diagnosis (ketosis precipitated by an infectious factor) but also the presence of hereditary antecedents of type 2 diabetes. The lack of regression of insulin requirements after remission of SARS COV-2 infection is also particular.

The evolution of insulin secretion and the maintenance of glycemic control in conditions of a low insulin requirement, for a relatively long period of time, in normal weight patients with markers of autoimmunity (anti-GAD antibodies) present, make it difficult to frame the type of diabetes not only in the traditional classification of diabetes, but also in the five clusters defined by Ahlqvist E. et al. [5].

The cases presented by us have characteristics such as diabetes with early onset, normal weight and the presence of anti-GAD antibodies, common to the first cluster reported by Ahlqvist E. et al., but, unlike patients in cluster 1, all three cases do not show marked insulin deficiency and have profiles glycemic in therapeutic targets on low doses of insulin after a long period from the diabetes onset.

The transitory clinical remission of type 1 diabetes usually occurs early after the onset of diabetes and typically lasts between 3 and 12 months [6, 7]. A potential explanation for transient remission is a reduction in glucotoxicity, by initiating insulin therapy, which induces an increase in endogenous insulin secretion from surviving beta cells [8, 9].

Several recent studies indicated residual beta cell function after more than 5 years following the onset of type 1 diabetes [10]. Prolonged maintenance of residual insulin secretion is associated with low risk of severe hypoglycemia, diabetic chronic microvascular complications and achievement of long term glycemic control [11–15].

The molecular mechanism underlying remission in type 1 diabetes is not fully elucidated. Certain factors including unfavorable cytokine profile, immune mediators, genetic markers, increased glucagon secretion, acidosis severity and younger age at diagnosis and cluster of diabetes-associated autoantibodies represent predictors of the occurrence and duration of clinical remission [16–19].

The clinical and biological characteristics of the presented patients are polymorphic, including both predictors of non-remission but, at the same time, of a long period of remission.

Conclusion

The presented cases highlight the existing pitfalls in establishing the diagnosis, as well as the challenges of choosing the optimal therapy in patients with type 1 diabetes, as the evolution can sometimes be atypical.

Conflicts of interest

The authors declare no conflict of interest.

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