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CASE REPORT

When Serum C-Peptide Measurement Drives Adequate Diabetes Mellitus Diagnosis and Therapy: A Case Report

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Abstract: ***Background*****:** Therapeutic targets in type 2 diabetes mellitus (T2D) are oriented towards nephron- and cardio-protection and the prescription of antihyperglycemic agents with proven renal and cardiovascular benefits are increasing over time. Failure to promptly diagnose insulinopenic diabetes may adversely affect the adequacy of treatment and have harmful consequences, including severe hyperglycemia and diabetic ketoacidosis.

Case Presentation**:** Herein we present the case of a 57-year-old woman referred to our clinic due to poor glycemic control (HbA1c 80 mmol/mol, therapeutic target <53 mmol/mol), class III obesity (BMI 41 kg/m2; normal value <25 kg/m^2), and high cardiovascular risk misdiagnosed with T2D several years before. C-peptide measurement (0.3 ng/dL; reference range 1.1 – 4.4 ng/mL) confirmed the diagnosis of an insulinopenic form of diabetes, and the islet autoimmunity was consequently measured (GADA 2,000 UA/mL, reference range <5 UA/mL; IA2 17.1 UA/mL, reference range <7.5 UA/mL) and defined the diagnosis of an autoimmune form of diabetes.

Discussion**:** Deprescribing insulin therapy in T2D patients in favor of other antihyperglycemic medications has become a growing therapeutic opportunity to provide adequate glucose control, promote weight loss, improve insulin sensitivity, and ameliorate cardiovascular and renal outcomes. However, a blunted insulin reserve poses significant restriction on the prescription of non-insulin agents (*e.g.*, diabetic ketoacidosis due to gliflozins). According to our experience, the routine testing of insulin reserve provides detailed information on diabetes pathophysiology with positive implications for the appropriateness of pharmacological prescriptions.

Conclusion**:** As part of our routine evaluation of diabetic patients, C-peptide measurement is a valuable and inexpensive tool to reclassify diabetes types and provide more appropriate disease management.

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1. INTRODUCTION

Type 2 diabetes mellitus (T2D) is a well-recognized chronic disease affecting millions worldwide and the foremost cause of diabetes in adults [1]. Type 1 diabetes (T1D) is a less prevalent insulinopenic type of diabetes with autoimmune pathogenesis that usually affects younger patients and requires lifelong insulin treatment [2]. Between these two diseases, a small percentage of patients have a slow-progressing form of insulinopenic diabetes, namely Latent Autoimmune Diabetes in Adult (LADA), which manifests as an intermediate phenotype between T1D and T2D, usually classified as T2D soon after diagnosis [3].

The diagnostic criteria of LADA are the same as for other forms of diabetes and, therefore, cannot offer a precise definition. The diagnosis of LADA should be suspected and then confirmed on the bases of clinical characteristics, biochemical markers of insulin reserve showing poor insulin secretion at steady state (*i.e.*, fasting c-peptide measurement), or after stimulation (*i.e.*, post-prandial or glucagon-stimulated c-peptide), and immunological parameters (*i.e.*, pancreatic autoantibodies) [4].

Herein we present the case of a 57-year-old woman diagnosed with T2D and class III obesity and at high cardiovascular risk (CVR) who attended our clinic due to poor glycemic control despite basal insulin treatment. As part of our routine practice, we emphasize the role of serum c-peptide measurement in providing a more accurate diagnosis and treatment of people with diabetes.

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2. CASE REPORT

A 57-year-old woman was admitted to the Department of University Internal Medicine due to poor glycemic control and class III obesity. Her family history was positive for T2D (mother and sister), myocardial infarction (mother), vitiligo, and celiac disease. She had been diagnosed with T2D in 2007 when she was 42 and started taking metformin 1,000 mg thrice daily. A few months later, she was admitted to an emergency department due to severe hyperglycemia, not complicated by diabetic ketoacidosis. A basal-bolus insulin regimen was introduced as an add-on to metformin 2,000 mg per day. She underwent regular diabetologist follow-up but never achieved optimal glucose control.

A few years later, other chronic comorbidities and complications were diagnosed: arterial hypertension and hypercholesterolemia (2016), cystoid macular edema with non-proliferative retinopathy (2020), mild-to-moderate non-alcoholic fatty liver disease, and mild carotid atheromasia (2021). She also underwent video-laparoscopic cholecystectomy due to cholecystic lithiasis in 2019, and she complained of significant weight gain over time, complicated by degenerative lumbar radiculopathy.

At our first evaluation, the body mass index (BMI) demonstrated class III obesity and a pathological waist circumference (127 cm; normal value <80 cm). Laboratory tests showed unsatisfactory glycemic control, preserved renal function, and a suboptimal lipid profile (Table **1**). Ongoing medications were as follows: 26 IU of long-acting (LA) insulin administered once daily at bedtime, 5 IU of short-acting (SA) insulin as a rescue therapy to correct severe hyperglycemia (>250 mg/dL), Metformin 1,000 mg twice-daily, Ramipril 5 mg, Acetylsalicylic acid 100 mg and Atorvastatin 10 mg per day.

The patient's phenotype and her personal clinical and pharmacological history did not raise suspicions about the previous diagnosis of T2D. Considering the elevated CVR, once-weekly subcutaneous Semaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1RA), was prescribed, SA insulin was discontinued, and LA insulin was down-titrated to gradually replace it with a sodium-glucose transporter type 2 inhibitor (SGLT2i).

As an established routine in our clinical practice, fasting serum c-peptide was measured to check the pancreatic β-cell reserve and ensure a safe prescription of antihyperglycemic agents. Fasting serum c-peptide was very far below the lower limit of the reference range (1.1 – 4.4 ng/mL, Table **1**), and, therefore, pancreatic islet autoimmunity was tested to exclude an autoimmune insulinopenic form of diabetes mellitus. The titers of both glutamic acid decarboxylase antibodies (GADA) and anti-tyrosine phosphatase-like insulinoma antigen 2 (IA2) were very high (normal values <5 and <7.5 UA/mL, respectively; Table **1**).

Table 1. Patient characteristics at baseline and during a short-term follow-up.

Laboratory Tests	Visit 1	Visit 2 (8th week)	Visit 3 (12th week)	Visit 4 (16th week)
HbA_{1c} (mmol/mol, therapeutic target <53 mmol/mol)	80	70	-	83
Fasting plasma glucose (mg/dL, reference range 70 – 100 mg/dL)	196	132	-	247
Fasting c-peptide (ng/mL, reference range 1.1 – 4.4 ng/mL)	0.3	-	-	0.1
Urine ketones (absent)	absent	absent	absent	absent
GADA (UA/mL, reference range <5 UA/mL)	2,000	-	-	-
IA2 (UA/mL, reference range <7.5 UA/mL)	17.1	-	-	-
Total Cholesterol (mg/dL, therapeutic target <200 mg/dL)	189	137	-	113
Low-density lipoprotein (mg/dL, therapeutic target <70 mg/dL)	114	68	-	48
High-density lipoprotein (mg/dL, therapeutic target >50 mg/dL)	59	56	-	52
Triglycerides (mg/dL, therapeutic target <150 mg/dL)	82	63	-	67
Serum creatinine (mg/dL, reference range 0.5 – 0.8 mg/dL)	0.5	0.68	-	0.5
Estimated glomerular filtration rate (CKD-EPI, ml/min/1.73 m^2, normal value >90 ml/min/1.73 m^2)	135	94.8	-	135
U-ACR (mg/g, reference value <30 mg/g)	<30	<30	-	-
Anthropometric parameters				
Body Weight (Kg)	108	92	88.5	84.5

(Table 1) contd….

Laboratory Tests	Visit 1	Visit 2 (8th week)	Visit 3 (12th week)	Visit 4 (16th week)
Body mass index (Kg/m^2, normal weight <25 kg/m^2)	41	35.1	33.7	32.2
Waist circumference (cm, normal value <80 cm)	127	123	-	110
Therapy	-	-	-	
Short-acting insulin (IU/day) (breakfast/lunch/dinner)	Rescue therapy*	Rescue therapy*	Rescue therapy*	(- / 4 / -)
Long-acting insulin (IU/day)	26	24	15	18
Metformin (mg/day)	2,000	500	500	500
Semaglutide (mg/week)	-	0.5	0.5	0.5
Atorvastatin (mg/day)	10	10	10	10

Note: HbA_{1c}: glycated hemoglobin; GADA: glutamic acid decarboxylase antibodies; IA2: anti-tyrosine phosphatase-like insulinoma antigen 2; not available -; discontinued: /* In the case of glycemia >250 mg/dL, self-administration of 5 IU of SA insulin analog was recommended.

The patient, therefore, received a diagnosis of LADA. Treatment was adjusted by reducing the metformin posology to 500 mg per day. Semaglutide 0,5 mg once-weekly was confirmed as an add-on to metformin and LA insulin to provide extra-glycemic effects such as promoting weight and visceral fat loss, reducing the overall CVR, and possibly preserving pancreatic β-cell reserve [5]. SGLT2i was not prescribed to avoid the risk of diabetic ketoacidosis.

The patient was advised to monitor blood glucose and ketones at home strictly and consider SA insulin in cases of postprandial glycemic levels > 250 mg/dL (Table **1**). She achieved better glucometabolic control over two months (HbA1c = -10 mmol/mol), with significant weight loss (-16 kg) and a concomitant decrease in daily insulin requirements over three months (Table **1**). After 16 weeks, a low dose of SA insulin was prescribed at lunch due to a further decline in β-cell reserve and consequent deterioration in glucose control. In the following weeks, Semaglutide was discontinued, and a basal-bolus regimen was reintroduced.

3. DISCUSSION

LADA is an autoimmune form of diabetes whose clinical hallmarks make it a bridge between T1D and T2D. It accounts for around 2-10% of all forms of diabetes. It should be considered in the differential diagnosis of patients over 30 years, with a family or personal history of autoimmunity, a lower number of associated comorbidities (arterial hypertension, overweight/obesity syndrome, dyslipidemia) at diagnosis, a slower decline in serum c-peptide over time compared to T1D, positivity for GADA or other pancreatic islet autoantibodies, and no insulin requirement at diabetes onset but a few months after that [4]. The clinical phenotype of LADA is very heterogeneous, but these patients are rarely overweight with a BMI usually intermediate between T1D and T2D [6] and inversely related to the severity of islet autoimmunity [7].

In this case, the age of diabetes onset, poor glycemic control, and early requirement of insulin therapy soon after the diagnosis could have argued in favor of an insulinopenic form of diabetes. However, this suspicion was only raised by the finding of almost undetectable fasting serum c-peptide, which provided evidence of a reduced β-cells reserve [8]. The high titers of GADA and IA2 then confirmed the autoimmune etiology of her diabetes.

In a comprehensive discussion about the role of c-peptide in driving the diagnosis, some aspects should be discussed. Serum c-peptide is susceptible to proteolytic cleavage and should be measured soon after the venous sample [9]. C-peptide clearance is attributable to renal excretion, and its serum levels may be overestimated in cases of renal insufficiency [9]. Moreover, the administration of exogenous insulin may affect baseline c-peptide secretion even if this mechanism depends mainly on the insulin dose and individual insulin sensitivity [10]. Fasting plasma/serum glucose levels are also necessary to interpret fasting c-peptide concentration. High glucose levels (*i.e.*, >140 mg/dL, reference range 70 – 100 mg/dL) provide adequate stimulation to endogenous insulin (and consequently c-peptide) secretion. Conversely, a low glucose concentration at the sample time may negatively affect insulin secretion, resulting in low c-peptide levels [11].

Our patient had normal renal function and, at the time of the first serum c-peptide measurement, was taking only 26 IU/day of LA insulin. Additional insulin boluses before the fasting serum c-peptide determination were correctly avoided on the sampling day. Fasting glucose levels were high at the time of samples (Table **1**), leading us to consider stimulated cut-off in interpreting c-peptide measurements. Given the patient's characteristics, it was reasonable assuming a state of insulin resistance. So the potential effect of exogenous insulin administration on serum c-peptide concentration was considered negligible [12].

In general, fasting serum c-peptide levels are associated with the diabetes type, being indicative of T1D when <0.2 nmol/L (0.6 ng/mL), and with its duration, and may predict the likelihood of response to both insulin and non-insulin treatments [9]. Fasting and stimulated c-peptide levels <0.2 nmol/L (0.6 ng/mL) are also considered an indicator of absolute insulin deficiency and inability to achieve glycemic control with non-insulin treatment [13]. According to the

American Diabetes Association / European Association of Study of Diabetes joint recommendations, an alternative to insulin treatments may be prescribed if a sufficient β-cell reserve is confirmed. In this case, the basal level of c-peptide fell into the zone of scanty insulin reserve (<0.3 nmol/L or 0.9 ng/mL; reference range 1.1 – 4.4 ng/mL), indicating that insulin therapy was essential [4]. A poor insulin reserve may abruptly induce gluco-metabolic control loss, especially when concomitant stressogenic events occur. Adequate education to carefully monitor glucose and ketones at home and to self-administer insulin rescue therapy as needed is critical in this context.

At the first presentation, insulin therapy was considered inappropriate for this patient, as no doubts about the T2D diagnosis were raised. Several mechanisms are implicated in maintaining hyperglycemia in T2D, including peripheral insulin resistance (especially at the adipose tissue and skeletal muscle level), enhanced hepatic glucose output, dampening pancreatic insulin and enteric incretin secretion, enhanced renal glucose re-uptake, loss of appetite control, high circulating levels of free fatty acids, intracell lipid accumulation (*i.e.*, ceramides), adipose tissue accumulation (especially in visceral districts), and systemic inflammation [14, 15]. A pathophysiological-based therapeutic approach was therefore considered. The need to achieve glucose control and adequate extra-glycemic effects (*i.e.*, weight loss, provide cardio- and nephron-protection) lead us to modulate background treatment accordingly. The incretin-based approach associated with metformin instead of a multi-daily insulin regimen was considered a more appropriate therapeutic option. SGLT2i might have been considered as an alternative treatment, too. However, based on the c-peptide value, we reclassified the inaccurate diagnosis of T2D, corrected our last treatment adjustment, and avoided the prescription of SGLT2i [4]. Although GLP-1RA cannot effectively replace long-term insulin therapy in patients with insufficient insulin reserve, Semaglutide was initially confirmed for its possible antiapoptotic activity on beta-cells and to provide extra-glycemic effects, as observed in T2D, such as weight loss, cardio- and nephron-protection [16]. However, it was finally discontinued in favor of a basal-bolus insulin regimen due to the lack of clear indication.

Despite controversy about the routine use of c-peptide measurement in clinical practice, especially because of concerns about the interpretation of c-peptide measurements, our group has previously highlighted its usefulness in redirecting a misdiagnosis, optimizing antihyperglycemic therapies in line with current targets, and allowing discontinuation of unnecessary insulin therapies [17, 18]. Other cases have also been published in the literature, providing anecdotal evidence of the utility of c-peptide measurement in the diagnostic workup of patients previously diagnosed with T2D: a 23-year-old man diagnosed with diabetes six months before and treated with a sulfonylurea (fasting c-peptide 1.9 ng/mL); a 71-year-old man diagnosed with diabetes two years before and on oral antihyperglycemic medications (fasting c-peptide <0.1 ng/mL; reference range 0.78 - 5.19 ng/mL); a 55-year-old woman diagnosed with diabetes one month before she discontinued a 9-month isotretinoin treatment due to acne (fasting c-peptide at the time of diagnosis 0.4 ng/mL; reference range 0.78 - 5.18 ng/mL); a 34-year-old woman with a two-year history of diabetes mellitus treated with metformin plus SGLT2i and admitted to an emergency department due to euglycemic diabetic ketoacidosis (fasting c-peptide 0.36 ng/mL; reference range 0.5 - 2 ng/mL) [19-22].

An extensive study has demonstrated that the random measurement of serum c-peptide allowed for reclassification of the diabetes type in 58 of 859 patients assessed (7%), resulting in treatment adjustments, insulin suspension, and significant economic benefits for the healthcare system [23].

CONCLUSION

This case report depicts an example of reclassification of the diabetes type based on fasting serum C-peptide measurement and treatment adjustment. Despite ongoing controversy, the routine use of c-peptide assay could be encouraged to improve the quality of care for diabetes mellitus.

AUTHORS' CONTRIBUTIONS

All authors contributed to the conception, data collection, synthesis and interpretation, manuscript drafting, and critical reviewing. All authors read the paper, approved the final version of the manuscript, and provided consent to publication.

LIST OF ABBREVIATIONS

BMI	=	Body Mass Index
GADA	=	Glutamic Acid Decarboxylase Antibodies
HbA1c	=	Glycated Hemoglobin
IA2	=	Anti-Tyrosine Phosphatase-Like Insulinoma Antigen 2
LADA	=	Latent Autoimmune Diabetes of Adults
T1D	=	Type 1 Diabetes Mellitus
T2D	=	Type 2 Diabetes Mellitus

CONSENT FOR PUBLICATION

The patient, adequately informed about the scientific purposes of this paper, provided written consent to publication.

STANDARD OF REPORTING

CARE guidelines were followed.

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CONFLICT OF INTEREST

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