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Case Report

Successful Use of a Combination of Two Long-acting Basal Insulin Analogs for the Treatment of Marked Insulin Resistance in Type 2 Diabetes Unresponsive to Standard Therapy

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Abstract

Insulin resistance is a major management challenge in patients with Type 2 diabetes (T2DM). A 62-year-old female patient with T2DM caused by insulin resistance is reported. Her hyperglycemia did not respond to conventional combinations of insulin therapy. However, she responded very well to a unconventional use of the combination of two basal insulin analogs with additional short-acting insulin. This approach needs confirmation and elucidation for a potential role in these not very uncommon cases.

Keywords: Basal insulins, diabetes, insulin resistance

Introduction

It is generally accepted that insulin resistance and beta-cell dysfunction are the two main factors involved in the development of type 2 diabetes (T2DM).[1] The relative contribution of insulin resistance versus beta-cell dysfunction on the pathogenesis of diabetes has aroused much debate.[1,2]

T2DM patients with marked insulin resistance can be a challenge to manage with the standard therapy of T2DM.[1,2] The pathophysiology of the disease from the development of autoantibodies to the insulin receptor, which causes severe insulin resistance, and its phenotype consisting of severe acanthosis nigricans, diabetes mellitus with severe hyperglycemia unresponsive to a massive doses of insulin, and hyperandrogenism in women.[2,3] It is an acquired form of severe insulin resistance, usually associated with other autoimmune conditions.[3,4]

A case of poor glycemic control due to severe insulin resistance not responding to the conventional antidiabetic therapy who was successfully treated with an unconventional therapy using combination of two second generation basal insulins with additional oral agents and prandial insulin is presented and discussed.

Case Report

A 62-year-old white Caucasian female patient with a recent diagnosis of T2DM presented to her primary care physician complaining of history of polydipsia, polyuria, and unintentional weight loss of 10 kg for 2 months. Her body mass index was 34 kg/m^2. Her random blood glucose (BG) at the time of diagnosis was 18.2 mmol/L, and hemoglobin A1c (HbA1c) level was 87 mmol/mol (10.1%). Her past medical history included hypertension and hyperlipidemia. She did not have any phenotypic features of insulin resistance such as acanthosis nigricans. Typical endocrine causes of insulin resistance including Cushing syndrome and acromegaly were excluded by the standard endocrine tests.

The patient was presumed to have T2DM, and she was started on oral antidiabetic medications. However, her poor glycemic control persisted for the following 6 months despite the treatment with progressively increasing doses reaching maximal doses of multiple oral hypoglycemic agents including metformin (1000 mg twice daily), pioglitazone (45 mg daily), a sulfonylurea (gliclazide 160 mg twice daily) in addition to

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a glucagon-like peptide-1 agonist (liraglutide 1.2 mg daily). She continued to experience symptomatic hyperglycemia. She was treated with different basal insulin regimens including both human and analog preparations 100 units/ml detemir (Novo Nordisk) and Glargine (Sanofi). She required about 800 units of insulin on a daily basis, and her capillary BG remained consistently high (persistently in double figures) with no variability in the BG readings. She was admitted a few times to hospital because of high BG, and she was treated with insulin infusion. During hospitalization, she required very high doses of insulin treatment (10 units/h with the continuation of long-acting insulin (detemir 300 units). The complete blood count, renal function, liver function test, insulin antibodies, and tumors markers, including carcinoembryonic antigen and cancer antigen 199, were normal [Table 1]. Computed tomography scan of the abdomen showed a normal pancreas [Figure 1].

Empirically, a combination of two second generation preparations of basal insulin including insulin Degludec 100 (Tresiba, Novo Nordisk) and Glargine (U300; Toujeo® before Sanofi Sanofi) in addition to Humalog Lispro 200 (200 units/ml; Eli Lilly) was used. She soon reported some improvement in both the hyperglycemic symptoms and self-monitoring of blood glucose values [Table 2]. Four months after treatment, the glycemic control improved dramatically; her osmotic symptoms resolved completely with lowering of HbA1c results to around 64 mmol/mol (8.0%) [Table 2]. Her insulin requirements decreased by more than 75% of her initial doses including both the long- and short-acting insulins. At the time of this report, she is on metformin Lispro (1000 mg twice daily), liraglutide (1.2 mg), insulin humalog (U200) 80 units daily with each meal and insulin degludec (40 units daily) given at 22:00 h and Glargine 25 units once daily (U300) given at 8:00 h in the morning. The calculated total daily dose of insulin therapy of 145 units compared to the previous insulin dose of 800 units daily. All insulin injections were delivered by pen devices.

Discussion

Contemporary treatment of T2DM is based on lifestyle modification and pharmacological therapy. Oral hypoglycemic medication for improving insulin sensitivity and pancreastic beta-cell dysfunction, starting with metformin, remains the first-line treatment for T2DM.[5] Our patient presented with very high BG readings with predictably marked osmotic symptoms. Her initial treatment failed to control her hyperglycemia despite using the combinations of therapy, which included both oral hypoglycemic agents and insulin fairly promptly.

In view of the poor response to the combination therapy and the need for unusually high doses of insulin, we considered using the new highly concentrated insulin preparation to explore if they can help to improve both BG control and insulin resistance by improving both insulin absorption and reducing variability as this will help to stimulate glucose uptake and metabolism in peripheral tissues.[6]

Table 1: Baseline investigations of the patient compared to the laboratory

Markers of metabolic control and autoimmunity	Patient data	Reference range
Hemoglobin A1c	175	36-47 (mmol/mol)
Fasting C-peptide	2.1	0.34-1.8 (nmol/L)
Fasting insulin	250	12-150 (Pmol/L)
Insulin antibodies	1	0-5 (mg/dl)
Glutamic acid decarboxylase antibody	<10	0-25 (U/ml)
Islet antigen-2 antibodies	<10	0-10 (U/ml)
Islet cell antibody	Negative	Negative
Serum total cholesterol	5.7	<4 (nmol/L)
Fasting serum triglyceride	6.4	<1 0.8 (nmol/L)
LDL cholesterol	1.2	<2 (nmol/L)
HDL cholesterol	3.2	>1.2 (nmol/L)
Ca199	13	0-37 (kU/L)
CEA	3	0-5 (ug/L)
ALT	18	0-40 (U/L)
ALP	100	35-120 (U/L)
Serum bilirubin	8	0-21 (umol/L)
Plasma albumin	37	34-50 (g/L)
eGFR	66	>70
Serum creatinine	77	50-110 (umol/L)
24-h urine free cortisol	181	0-380 (nmol/24 h)
Serum growth hormone	< 0.1	<0.1 (ug/L)
Serum IGF-1	12	4-23 (nmol/L)

LDL: Low-density lipoprotein, HDL: High-density lipoprotein, CEA: Carcinoembryonic antigen, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, eGFR: Estimated glomerular filtration rate, IGF-1: Insulin-like growth factor 1

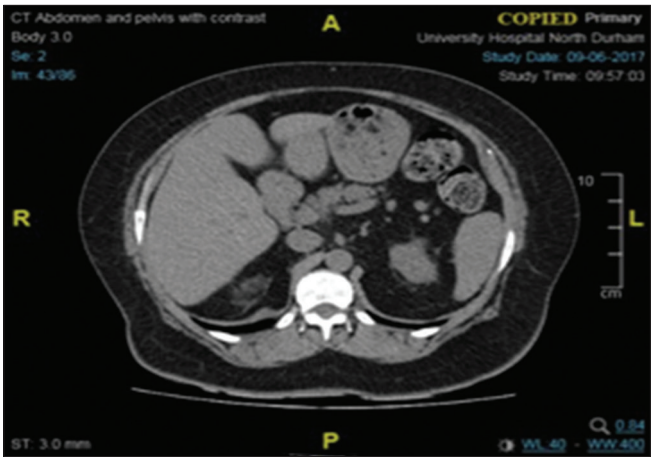

Figure 1: Computed tomography abdomen

Glargine (U300) is a new formulation of glargine resulting in a flatter and more prolonged time–action profile than Glargine (U100). Insulin degludec is an ultra-long-acting insulin analog, which forms long subcutaneous multi hexamers that delay absorption. Insulin degludec has a flat, stable glucose-lowering profile with a duration action of more than 42 h, and less within the patient's day-to-day variability in the glucose-lowering effect.[6-8]

The second generation basal insulin analogs have used upconcentration in addition to precipitation (insulin glargine

Table 2: Time scale of the various medications used, blood glucose ranges, and hemoglobin A1c

	Date								
	April 5, 2016	July 10, 2016	October 15, 2016	January 10, 2017	April 4, 2017	June 5, 2017	August 15, 2017	October 20, 2017	January 10, 2018
Metformin 1 gram BID	+	+	+	+	+	+	+	+	+
Liraglutide 1.2 mgs daily	+	+	+	+	+	+	+	+	+
Pioglitazone 45 mgs	+	+	+	-	-	-	-	-	-
Glargine 100	-	-	-	+	-	-	-	-	-
Humalog lispro 200	-	+	+	+	+	+	+	+	+
Detrimer 100	-	+	-	-	-	-	-	-	-
Dedgludec 100	-	-	-	+	+	+	+	+	+
Glargine 300	-	-	-	+	+	+	+	+	+
BG (mmol/L)	15-20	18-22	20-26	25-30	25-30	14-25	15-20	13-17	7-10
HbA1c mmol/mol	78	115	130	170	175	160	130	80	64

BG: Blood glucose, HbA1c: Hemoglobin A1c, +: treatment given, -: treatment not given

U300), and multihexamer formation in addition to albumin binding (insulin degludec), to further increase the duration of action and/or decrease the day-to-day variability of the glucose-lowering profile. This change confers a slower rate of absorption to degludec by enabling the formation of high-molecular-weight complexes, and albumin-binding after subcutaneous injection. Degludec forms highly stable dihexamers (closed configuration) in phenol- and zinc-containing formulation as a result of an interaction between one of the fatty diacid side chains of one hexamer and a zinc atom of another.[9-11] A duration of action that extends beyond 24 h in both insulins is advantageous as it means that with once-daily dosing, circulating insulin concentrations will rise over a few days until a steady-state profile with a low peak: trough ratio is reached. This reduces waxing and waning of effect, thereby reducing the risk of hypoglycemia.[12]

There are neither any trial evidence nor any anecdotal reports to the best knowledge of the author. However, the choice was based on the pharmacodynamics and kinetic advantages of both insulins in combination. The patient responded well following the addition of high concentrated basal insulins and her BG reading improved within a few weeks, and this was reflected in a better HbA1c values. Later on, the insulin requirements decreased as her BG control continued to improve.

The possible underlying mechanism for improvement in BG control is more likely related to the fact that both basal novel insulin are binding to different sites within insulin receptor and with different affinity and this will help to increase glucose uptake in the peripheral tissues, and they suppress hepatic glucose production. This will help to improve both insulin sensitivity and BG control as reflected by the reduction of significant doses of both short- and long-acting insulin doses.[6,8,9]

Conclusion

Insulin resistance can be a challenge to manage with standard therapy in patients with T2DM. Our patient responded well to the combination of two different novels basal insulin and the resolution of the metabolic abnormalities. To the best of the author's knowledge, this is the first case of marked insulin resistance successfully treated with a combination of two novel basal insulin analogs. This case indicates that the combination of the second generation basal insulin degludec (U200) and insulin Glargine (U300) improved insulin resistance, and it is a potentially useful insulin treatment option in diabetic patients with marked insulin resistance. Further studies are required to confirm this finding and to hypothesize and further elucidate possible mechanisms of action.

Declaration of patient consent

The author certifies that he has obtained all appropriate patient consent forms. In the form, the patient has given her consent for her clinical information to be reported in the journal. The patient understands that her name and initials will not be published and all due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Author's contributions

Single author.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No prior ethical approval is required at our institution for single case reports. However, the patient provided consent for publication as stated above.

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