

Severe Hyperglycemia in an Insulin-Deficient Patient with Type 2 Diabetes Responding Well to Oral Antidiabetic Therapy

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Abstract

Type 2 diabetes mellitus (T2DM) is a chronic, progressive disease characterized by a steady decline in beta-cell function and insulin resistance. As a result, most patients with T2DM may require treatment with insulin after 15–20 years of diagnosis. Various pathophysiological defects were identified leading to hyperglycemia, including reduced insulin secretion due to beta-cell failure. They reduced beta-cell mass and a defect in insulin secretion, which leads to a relative insulin deficiency in these patients requiring insulin treatment. Most international guidelines recommend starting insulin treatment in patients with poor glucose control, mainly if the glycated hemoglobin (HbA1c) is above 9% with the presence of symptoms, especially in relatively newly diagnosed patients with T2DM. We present a 45-year-old patient with T2DM of 5 years duration who attended our center with severe hyperglycemia with evidence of insulin deficiency both clinically and biochemically, who responded well to oral antidiabetic agents achieving adequate glycemic control.

Keywords: Glucose toxicity, glucotoxicity, insulin deficiency, insulin treatment, type 2 diabetes

INTRODUCTION

The American Diabetes Association/European Association for the Study of Diabetes consensus on the management of hyperglycemia in type 2 diabetes mellitus (T2DM) recommends metformin as the first-line treatment for patients with T2DM unless there are contraindications in lifestyle modification. Metformin is the first-line therapy due to its effectiveness, safety, lower cost, and favorable cardiovascular benefits. Subsequent choice of a suitable antihyperglycemic therapy depends on the presence of established cardiovascular disease,

chronic kidney disease, or heart failure, in which case GLP1-RA and/or SGLT2 inhibitors are recommended after metformin while in the absence of such comorbidities. The treatment choice is based on whether there is a compelling need to avoid hypoglycemia, avoid weight gain, or promote

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weight loss or cost.^[1] The report also highlighted the importance of a patient-centered approach to guide the choice of diabetes treatment.

Whether oral hypoglycemic agents can be used as a first-line treatment for patients presenting with severe hyperglycemia is a valid question many clinicians face in their daily practice. According to most international guidelines, these patients should be considered for insulin treatment. However, there are some differences among guidelines on the glycated hemoglobin (HbA1c) thresholds for starting insulin; for example, the American Association of Clinical Endocrinologists and American College of Endocrinology recommend insulin initiation in patients with HbA1c >9.0%.^[2] On the other hand, the UK National Institute for Clinical Excellence recommends insulin treatment in patients with HbA1c >7.5% despite dual oral therapy.^[3]

In our clinical practice, many patients are reluctant to consider insulin treatment despite poor glycemia. This is due to the stigma associated with insulin therapy. We report a patient with T2DM of 5 years duration who presented with severe hyperglycemia, significant weight loss, and clinical and biochemical evidence of insulin deficiency, who refused insulin therapy but responded well to oral hypoglycemic agents.

CASE REPORT

A 45-year-old man, single, who works as a mechanic, was diagnosed with T2DM in July 2015. His diabetes was diagnosed accidentally during hospital admission for urinary sepsis. While an inpatient, he received insulin treatment but discharged on metformin only due to his refusal of insulin treatment. He was advised to attend a diabetes clinic for review, but he was lost to follow-up and presented to our center in July 2020. At this time, he was taking metformin 500 mg three times daily. He claimed that he was compliant with treatment, and he denied polyuria, polydipsia, or tiredness but has lost a significant amount of weight. Before his diabetes diagnosis in 2015, his weight was 84 kg, but he weighed only 42 kg upon first seeing us. He has no family history of diabetes, a review of systems revealed no significant findings,

and systemic examination was unremarkable apart from obvious cachexia.

His initial biochemical profile showed blood glucose value of 20 mmol (360 mg/dl) with HbA1c of >16.0% (155 mmol/mol), C-peptide of 0.1 nmol/l (0.37–1.47), fasting insulin level of 0.886 µU/ml (2.6–24.9), GAD antibodies of <5.0 U/ml (0.0–5.0), and IA-2 autoantibodies of 7.5 U/ml (<7.5 = negative). The rest of his blood evaluation is shown in Table 1. DNA sequencing showed no mutation on sequence analysis of HNF1A, HNF4A, and GCK genes. Based on the above findings, we recommended insulin treatment. Unfortunately, the patient declined insulin despite our repeated attempts to convince him. Therefore, he was started on gliclazide MR 120 mg/day and advised to continue on metformin. He was advised to attend the emergency department (ED) if he became unwell and was given an appointment to come back to our diabetes clinic with blood glucose readings in 1 week.

He did not keep his appointment but was contacted over the phone. He reassured us that he is doing well, and his blood glucose readings are coming down, to return to our clinic in 2 months. In return, he had significant improvement in his symptoms, and his blood glucose readings were much improved. His HbA1c was 8.6% (initial HbA1c >16.0%). This was associated with an improvement in his body weight to 45.8 kg during his last clinic visit. He developed significant painful diabetic neuropathic symptoms affecting both feet, which were severe enough to interfere with his sleeping and daily activities. Examination confirmed bilateral sensory loss with no wasting or motor signs; peripheral circulation

Table 1: Baseline investigations

Investigations	Reference values	Result
Hemoglobin	70-180 g/l	128
Creatinine	59.0-104 µmol/l	55
Estimated glomerular filtration rate	>90 ml/min/1.73 m ²	120
Alanine aminotransferase	<41 IU/l	48
Aspartate aminotransferase	<40 IU/l	30.5
Total cholesterol	<5.2 mmol/l	5.89
Low-density lipoprotein cholesterol	<2.6 mmol/l	3.5
Albumin creatinine ratio	<30 mg/g	<30
Thyroid stimulating hormone	0.27-4.2 mIU/l	1.28

was normal. He was prescribed pregabalin to control his neuropathic pain. At this point, his retinal examination showed no evidence of retinopathy. Two months later, he was reviewed again. He continued to do well with further improvement in his glucose control; his HbA1c in his last visit was 7.2%, C-peptide was 0.39 nmol/l (0.37–1.47), and fasting insulin level was 17.92 pmol/l (20.8–173.6) on metformin and gliclazide only. His neuropathic symptoms resolved completely, and a further follow-up was arranged in 3 months.

DISCUSSION

T2DM is a chronic progressive disease, the hallmark of T2DM is beta-cell failure and insulin resistance with resultant hyperglycemia, and the hyperglycemia in itself can negatively impact beta-cell function with further exacerbations of hyperglycemia, a process referred to as glucotoxicity.^[4]

We presented a 49-year-old gentleman with a 5-year history of T2DM and no family history of diabetes who presented with severe hyperglycemia and significant weight loss. He refused to accept insulin as the best available treatment option despite clinical and biochemical evidence of insulin deficiency. He has no family history of diabetes. Negative pancreatic autoantibodies excluded type 1 diabetes and genetic forms of diabetes, and no common MODY DNA mutations were detected. He responded well to metformin and sulfonylureas (SUs) with significant improvement in all parameters, including recovery of his beta cells, evidenced by improved C-peptide and insulin levels [Table 2].

Glucose toxicity is a well-known phenomenon in diabetes that is not well understood, and it adversely affects beta-cell function in addition to the well-known relative insulin deficiency and insulin resistance in T2DM. Hyperglycemia may negatively

affect beta-cell mass by inducing apoptosis without a compensatory increase in beta-cell proliferation and neogenesis. The detrimental effect of excessive glucose concentrations is referred to as glucose toxicity. The ability to secrete adequate amounts of insulin is determined by beta-cell functional integrity and overall mass. Glucose, the primary regulator of insulin secretion and production, exerts adverse effects on the beta-cell function when present in excessive amounts over a prolonged period.^[5]

Robertson *et al.* concluded that glucose toxicity and glucose desensitization concepts should be differentiated because they have very different significance. The mechanism of action for glucose desensitization seems most likely to be expressed at the exocytotic insulin apparatus or insulin stores within the beta-cell level. In contrast, the mechanism of action for glucose toxicity may be at the level of insulin gene transcription. This differentiation raises the possibility that exposure of patients to chronic hyperglycemia may cause toxic glucose effects on the process of insulin gene transcription and/or expression that are irreversible. If so, this may contribute to the so-called secondary drug failure and in any event re-emphasizes the need to intensify therapeutic efforts to improve glycemia in T2DM.^[6]

Somewhat surprising in our case, the patient did not experience any osmotic symptoms despite the extreme hyperglycemia, allowing the homeostatic adaptation of the body to high blood glucose levels. We expected him to exhibit at least some osmotic symptoms, which he denied, though he lost significant weight. He has no proteinuria or evidence of microangiopathy elsewhere.

Our patient responded well to SUs despite the initial evidence of insulin deficiency, which was prescribed only because he refused to accept insulin. Refusal of insulin is common in clinical practice due to

Table 2: Improvements in glucose control and beta-cell parameters

Investigations	Reference values	July 2020	September 2020	November 2020
Glucose	mmol/L*	19.8	7.1	8.4
HbA1c	<7%	16.5	8.69	7.23
Fasting plasma insulin	(20.8-173.6 pmol/L)	6.36	24.69	17.92
Serum C peptide	(0.37-1.47 nmol/L)	0.185	0.48	0.39
HbA1c: Hemoglobin A1c				

many factors, most commonly, fear of injections and hypoglycemia. Most international guidelines recommend insulin treatment for patients with newly diagnosed diabetes and blood glucose values persistently above 300 mg/dL and/or HbA1c above 9%, in addition to the well-known phenomenon of escalating the treatment to insulin in patients with progressive deterioration in glycemia, despite multiple oral agents and HbA1c of >7.5%.

It is well known that SUs exert their action by stimulating beta cells to secrete insulin. In the presence of beta-cell failure, we would expect no effect of SUs on glucose levels. In our case, we had all the evidence to suggest that he is insulin deficient, clinically and biochemically. His insulin and C-peptide levels on presentation were almost undetectable [Table 1]. Despite that, we started him on SUs only because he refused insulin therapy, expecting him not to respond and possibly to present with ketoacidosis shortly. Instead, surprisingly, his glycemia started to improve steadily but slowly on biguanides and SUs in combination with subsequent recovery of his beta-cell function, evident by rising C-peptide and insulin levels. SUs stimulate insulin secretion from beta cells with an expectant rise of C-peptide and insulin level, inferring that he had a degree of the beta-cell reserve, but the extreme and persistent hyperglycemia further suppressed his beta cells through the effect of glucose toxicity.^[7]

It is not uncommon for patients with T2DM to present with severe hyperglycemia with varying degrees of symptoms, ranging from mild polyuria and polydipsia to more severe osmotic symptoms with substantial weight loss. The majority of international diabetes societies recommend insulin treatment for patients with T2DM presenting with severe hyperglycemia in the presence of osmotic symptoms. Adequate data on the effect of oral hypoglycemic agents on patients presenting with severe hyperglycemia is lacking. One retrospective study demonstrated that oral hypoglycemic agents are as effective as insulin in achieving good glycemic control.^[8] Emergency department (ED) use of the SU (glipizide) to treat patients presenting with severe hyperglycemia has been studied in an open-label randomized controlled trial in patients presenting to ED with blood glucose

levels between 300 and 700 mg/dl, and the study showed that use of glipizide is as effective as insulin in this group of patients.^[9] The use of other oral hypoglycemic agents such as DPP4 inhibitors has been studied in an open-label randomized controlled trial of 100 patients with severe hyperglycemia to receive either SU (glipizide) or a single-pill combination (SPC) saxagliptin/metformin. Both approaches were shown to be effective with less hypoglycemia in the saxagliptin/metformin SPC.^[10]

In clinical practice, insulin treatment for patients presenting with severe hyperglycemia is not without challenges; patient's reluctance to initiate insulin, stigma, fear of hypoglycemia, phobia from injections, and lack of time and resources to support insulin use are all challenges clinicians face in their daily practice.^[8] Our patient refused to take insulin despite the clinical and biochemical evidence of insulin deficiency, but somewhat surprisingly, he responded well to SUs in combination with biguanides; the latter, he has already been taking before. This illustrates the need to study each case separately while referring to the guidelines to treat patients with T2DM.

CONCLUSIONS

Insulin treatment is often required at some point in the management of hyperglycemia in patients with T2DM. It may be needed as an initial treatment in some patients to control extreme hyperglycemia and avoid hyperglycemic emergencies, particularly in newly diagnosed patients with diabetes. The present case of T2DM with severe hyperglycemia and clinical and biochemical evidence of insulin deficiency responded well to oral agents after refusal of insulin treatment, with subsequent recovery of his pancreatic beta-cell function.

Declaration of patient consent

The authors certify that they have obtained the appropriate patient consent form. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that no names and initials will be published, and all due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Authors' contribution

All authors were involved in the clinical care of the patient, drafting and revisions of the manuscript, and they have all approved its final version.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No prior ethical approval is required for single case reports. However, the patient provided consent for publication.

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