PAMJ Clinical Medicine
Pan African Medical Journals

Case report

A case of insulin antibody-mediated insulin resistance in type 2 diabetes treated by glucocorticoid

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Received: 17 Oct 2019 - Accepted: 21 Nov 2019 - Published: 03 Dec 2019

Domain: Endocrinology

Keywords: Diabetes mellitus, glucocorticoids, insulin, insulin antibody, insulin resistance

Abstract

The syndromes of severe Insulin resistance (IR), although rare, are very interesting and clinically important. It causes a deterioration of the glycemic control, despite the very high dose of insulin. One of the rarest etiologies is autoimmunity especially the production of insulin autoantibody. We report the case of a 61-year-old woman with a history of type 2 diabetes for 10 years. She has reported a deterioration of her glycemic control despite an increase in the dose of insulin up to 200U/day (d). The clinical examination was without particularity. There was no history of drug intake. A high titer of insulin antibodies was detected in the serum 77.6%. Prednisolone was administered with a dose of 0,5mg/Kg/d for 1month. The dosage was tapered 5mg at 15 days intervals until 5mg/d. Insulin requirement decreased by 66% and glycemic control was reached. The treatment of antibody-mediated IR is not standardized; corticosteroid therapy often gives good results.

Case report | Volume 1, Article 40, 03 Dec 2019 | 10.11604/pamj-cm.2019.1.40.20684

Available online at: https://www.clinical-medicine.panafrican-med-journal.com/content/article/1/40/full

Introduction

Insulin resistance (IR) is a common metabolic abnormality, defined by the decrease in the biological response to insulin. It occurs in association with a variety of physiological and pathophysiological situations such as puberty, pregnancy, obesity, polycystic ovary syndrome, liver steatosis, noninsulin-dependent diabetes mellitus, and metabolic syndrome [1]. It is also associated with all situations of increased secretion, whether primitive or secondary, of glucocorticoids, catecholamines or growth hormone. The syndromes of severe IR, although rare, are very interesting and clinically important. They have been described over the past 40 years [2,3]. These syndromes contributed to explore and understand the mechanisms of insulin action and resistance [4]. The etiologies of severe IR are diverse, but in most cases, the cause is not known. One of the rarest etiologies is autoimmunity, which is associated with high mortality [5]. It is mainly associated with type B IR, which results from autoantibody formation against the insulin receptor, but also insulin autoantibody (IAA) that is another rare autoimmune mechanism for severe hyperglycemia. The presence of IAA against exogenous insulin in diabetic patients was first described in 1956 by Berson [6]. It was common that the insulin was extracted from animals (pancreases of cows and pigs) to treat diabetes. At that time, exogenous IAA was present in greater than 95% of the patients [7]. In 1978, a human form of insulin was developed. Since that day, a decrease in the prevalence of IAA has been observed especially after the introduction of highly purified insulin analogs [8]. Herein we report the case of a patient, with type 2 diabetes, presenting a severe IR syndrome due to the production of IAA. Further, we have reviewed the available literature to discuss the clinical manifestations, the diagnosis, the prognoses, and the available treatment modalities.

Patient and observation

We report the case of a 61-year-old woman with a history of type 2 diabetes treated with human insulin for 10 years. She developed insulin resistance and she was admitted to our hospital in 2012. She was diagnosed as having diabetes mellitus in May 2008 by an inaugural ketosis, and her glycemic control was initially satisfying (HbAlc 7.7%) with a daily dose of 50 U/day (0.9 UI/Kg/d) of insulin. Since 2011, she has reported a deterioration of her glycemic control despite an increase in the dose of insulin up to 200 U/day (from 0.9 UI/Kg/d to 5.61 UI/Kg/d). When she was referred to our hospital, her fasting plasma glucose was over 3g/l, associated with many nocturnal hypoglycemia. Example of a glycemic cycle of our patient: 8h: 3.2 g/l /12h: 4.73 g/l / 16h: 4.16 g/l / 20h: 2.2 g/l / 22h: 2.9 g/l / 4h: 0.73 g/l. Her body weight and her BMI are respectively 54 kg and 23.68 Kg/m^2. She reports a weight loss of 6kg in one year (figure 1). There was no history of drug intake. Acanthosis nigricans was absent, and she had not subcutaneous nodules at insulin injection sites. There were no signs of hyperandrogenism (hirsutism, oligomenorrhea, infertility...). Syndromes associated with counter-regulatory hormones were not present, such as Cushing's syndromes (Cortisol cycle: t8h = 137ng/ml, t16h = 71 ng/ml, 2 mg 48-h dexamethasone suppression test: 8 ng/ml), acromegaly (GH: 3.9 mIU/l, IGF1: 55 µg/l (94 - 225 µg/l), hyperthyroidism (FT4: 18.2pmol/l, TSH: 1µUI/ml), and pheochromocytoma (no hypertensive crisis, Systolic blood pressure: 100 - 110mmHg without treatment). Liver steatosis has been eliminated. A high titer of insulin antibodies was detected in the serum 77.6%. However the test for anti-insulin receptor auto antibodies was not done in the absence of evocative context. Therefore we switched the treatment to the insulin analog (detemir/glulisine) with the aim of minimizing immunogenicity. After 2 months of treatment, the daily dose of insulin increased from 235 UI/d to 371 UI/d (6.88 UI/Kg/d) without obtaining glycemic control (Figure 1). There was no cause of deterioration of her glycemic control.

Then we decided to use steroid therapy associated with vildagliptin and metformin. Prednisolone was administered with a dose of 0,5 mg/Kg/d for 1 month. The dosage was tapered 5 mg at 15 days intervals until 5mg/d. Insulin requirement decreased by 66% and glycemic control was reached: fasting glucose was about 1g/l (Figure 2). In January 2017, she was readmitted for increasing dose of insulin and deterioration of glycemic control. A high titer of total insulin was detected (5642 pmol/l), whereas free insulin was 283pmol/l, suggesting that most of the exogenous insulin was bound to IAA and neutralized. The dose of prednisolone was increased again to 0,5mg/Kg/d. Fasting blood glucose and HbA1c levels were promptly decreased (from 12.5% to 6.4% after 7 months) as well as the daily dose of insulin (from 3.57 IU/kg/d to 1.8 IU/kg/d). Anti-insulin antibody rate has not been controlled.

Discussion

Insulin resistance is defined as a state (of a cell, tissue, or organism) in which there is a decrease of the biological response to insulin. Clinically, it manifests as a deregulation of glycemic homeostasis [2]. The measurement of insulin resistance is not always obvious. The glucose clamp technique is considered as the best available method, in its euglycemic version, but it is time demanding and technically challenging. Thus, in the research setting, we use frequently simpler methods to measure insulin sensitivity [9]. Nevertheless, for diabetics treated with insulin, the clinician can simply calculate the total dose of insulin per day as a measure of insulin sensitivity [9]. In the case of type 2 diabetes, some have defined severe insulin resistance as a dose of insulin >2 U kg/day [4,9,10] (Table 1) [9]. The threshold of a dose >200 U of insulin per day has abounded, given the epidemic of obesity, and the increase in the insulin dose significantly on body weight. Therefore, a dose>2 U/kg/day is currently used [5,9]. Autoimmunity is a rare etiology of severe insulin resistance, especially by IAA [5]. It is defined by the production of AA directed against exogenous insulin. The prevalence of these AA has decreased, since the use of recombinant human insulin or highly purified insulin analogs, but it is still a common condition [4]. It is estimated at about 40% of diabetic patients treated with human insulin [7,11]. Although, generally the antibodies are not clinically significant, high titers can cause adverse outcomes including extreme insulin resistance, unpredictable hypoglycemia and hypersensitivity reactions [5]. Our review identified 118 cases of type B insulin resistance and 12 cases of IAA-mediated insulin resistance in diabetics treated with human insulin [5]. Type B IR is often seen in black females and is characterized by significant weight loss, hyperandrogenism in females and diffuse acanthosis nigricans. It is usually associated with rheumatologic conditions. Biologically, it may be distinguished by a low triglyceride level and an adiponectin level greater than 7mg/L [5] which differs from the clinical picture of our patient. In contrary, IAA-mediated insulin resistance is more common in men and it occurs in an equitable manner regardless of the diabetes type [5]. Unfortunately, in the literature, almost every insulin antibody-mediated insulin resistance cases did not discuss clinical signs of hyperandrogenism, acanthosis nigricans, positive rheumatologic serologies, and variation of triglycerides or adiponectin [5]. Probably it is rarely associated with clinical or biological abnormalities [5] (the case of our patient). The antigen is usually human insulin but in some cases, it may be insulin analogs [5]. The diagnosis is confirmed when the serum sample is IAA positive and the value exceeds 5% [12], or the finding on radioimmunoassay analysis that the concentrations of total insulin were very high compared to a very low concentrations of free insulin, suggesting that most of the exogenous insulin were bound to IAA [12]. Insulin resistance, in this case, is explained by massive volumes of insulin binding to the insulin antibodies that reduce insulin action, thus triggering hyperglycemia (tampon-like effect) [12] On the other hand, rare nocturnal and fasting hypoglycemia can occur. Indeed, IAA could enhance and prolong the

pharmacodynamics action of insulin by the cleavage of insulin antibodies, so free insulin increases all at once (reservoir-like effect) [12]. This was the case of our patient, who had nocturnal and fasting hypoglycemia.

The mechanism of the production of exogenous insulin AA is still unknown [13]. But several factors are reported to influence this mechanism: purity and species of insulin [13]; the mode of insulin administration: the insulin pumps increase the risk for development of IAA in some patients [14]; genetic factors: the HLA genotype would play a role in presenting insulin peptides to T cells [4]. The HLADR7 subtype is a risk factor, and it is associated with a higher rate of IAA. Whereas, being homozygous HLA-B8, DR3 and C4AQ0 could be protective [4]; additive (zinc, protamine); storage conditions [11]; age: Immunological competence regresses as an individual ages, making decreased capacity to form high-affinity antibodies [12]. Concerning the treatment, until now there has been no any particular therapy evaluated in large randomized clinical trials [5] and no standardized therapy exists [5]. Less severe cases are treated in some reports by changing the human insulin [15] to insulin analogs which are less immunogenic. It was noted that insulin analog Lispro tread successfully that immunological insulin resistance and reduces IAA [15]. Treatment with insulin analog Glargine was also tested [16]. However, recently, Hattori *et al*. [17], have proved that insulin glargine and aspart are more antigenic than other insulin analogs. Other researchers have proposed treatment by cessation of insulin administration and switching to oral antidiabetic agents (OAD) when the endogenous insulin secretion is conserved [13]. It was noted that plasma insulin antibodies concentrations have significantly been lowered by the using of metformin combined with α-glucosidase inhibitor [18]. The exact mechanism of action was unclear; one of the possible explanations is that OAD may enhance the action of free insulin, and promote IA-immune complexes dissociation [12]. There was no study evaluating the effect of vildagliptin in IAA-mediated insulin resistance, it can be efficient for its insulin-sensitizing effect. On the other hand, severe cases require generally immunomodulatory therapies like glucocorticoids, similar to our patient. Indeed, glucocorticoids may inhibit the production of IAA and favor the dissociation of the IA-immune complex. We can also use rituximab, intravenous immunoglobulin, and sometimes plasmapheresis [5]. Different treatments used for AAI mediated immunological insulin resistance and hypoglycemia [19]; cessation of insulin administration [13]; glucocorticoids [19]; glucocorticoids/plasmapheresis [19]; glucocorticoids/immunosuppressant/plasmapheresis [20]; immunosuppressant/plasmapheresis [19]; glucocorticoids /insulin linspro [19]; insulin lispro [15]; insulin glargin [16]; insulin glulisine [19]; insulin glulisine/cessation of long-acting insulin analogs [19]; glucocorticoids/metrormin/vildagliptine: our patient. Long-term prognosis in this pathology, especially recurrence risk, has not been studied [15], and despite its rarity, it can be associated with high mortality [5]. However, if the diagnosis is early recognized and the treatment is well-conducted, the prognosis can be improved [5].

Conclusion

Antibody-mediated IR is a rare condition that causes, not only a deterioration of the glycemic control, despite the very high dose of insulin (>2U/Kg/d), but also an increase in morbimortality. The diagnosis is based on the clinical picture: severe IR with alternating postprandial hyperglycemia and nocturnal hypoglycemia, and the detection of IAA in the serum >5%. The treatment is not standardized; corticosteroid therapy often gives good results.

Competing interests

The author declare no competing interest.

Authors' contributions

Ben Salah Dhoha, Elleuch Mouna and Mnif Fatma: substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data. Rekik Nabila and Mnif Mouna: drafting the article or revising it critically for important intellectual content. Abid Mohamed: final approval of the version to be published. All the authors have read and agreed to the final manuscript.

Table and figures

Table 1: insulin dose requirements through different types of diabetes

Figure 1: changes in weight, average blood sugar and dose of insulin since the discovery of diabetes and with insulin analog

Figure 2: the effect of glucocorticoid on changes in dose of insulin and glycemic control in our patient with positive insulin autoantibody

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Table 1: insulin dose requirements through different types of diabetes

	Insulin doses		
	TDID (U/kg/d)	**TDID (U/d)**	
T1D typical insulin requirements	<1	<100	T1D normal insulin sensitivity
T2D typical insulin requirements	1-2	<200	T2D typical insulin resistance
High insulin requirements	2-3	200-300	Severe insulin resistance
Very high insulin requirements	>3	>300	Extreme insulin resistance

TDID: total daily insulin dose, T1D: Type 1 diabetes, T2D: Type 2 diabetes

Figure 1: changes in weight, average blood sugar and dose of insulin since the discovery of diabetes and with insulin analog

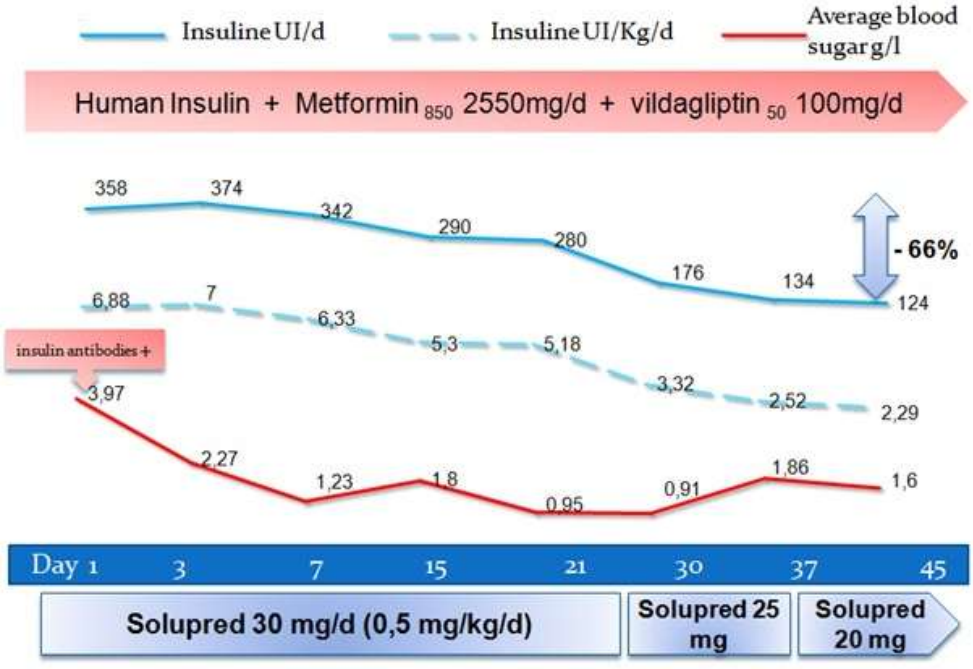

Figure 2: the effect of glucocorticoid on changes in dose of insulin and glycemic control in our patient with positive insulin autoantibody