Case Report

Late Systemic Lupus Erythematosus-Associated Insulin Resistance Syndrome: A Rare Cause of De Novo Diabetes Mellitus

José C. Alvarez-Payares 1, 1 Daniel Ribero 1, 1 Luis Rodríguez 2, 2 Carlos E. Builes 2, 2 Carolina Prieto, 2 Clara Arango, 2 Juan G. Gamboa, 3 and Cristian Alvarez-Payares 4

1Department of Internal Medicine, Universidad de Antioquia, Medellín, Colombia
2Department of Endocrinology and Metabolism, Hospital Pablo Tobon Uribe, Medellín, Colombia
3Department of Internal Medicine, Hospital Pablo Tobon Uribe, Medellín, Colombia
4Universidad de Sucre, Sincelejo, Colombia

Correspondence should be addressed to José C. Alvarez-Payares; josecarlosalvarez9@hotmail.com

Received 28 June 2022; Accepted 6 October 2022; Published 14 October 2022

Academic Editor: Bruno Megarbane

Copyright © 2022 José C. Alvarez-Payares et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The association of type B insulin resistance syndrome (TBIRS) due to autoimmune diseases such as systemic lupus erythematosus (SLE) is uncommon. This is partly due to the lack of established criteria for the diagnosis of this resistance. However, some clinical aspects may suggest that the diagnosis does not necessarily have to be positive insulin receptor antibodies as such patients could respond to immunosuppressive treatment. Methods. We describe a case and have performed a literature review on PubMed/MEDLINE, EMBASE, and Google Scholar bibliographic databases to identify all case reports. All available studies from January 1975 through December 2020 were included. Data collected were tabulated, and outcomes were analyzed cumulatively. Results. Thirty-one cases of TBIRS associated with SLE have been described. These patients presented with catabolic symptoms and hyperglycemia in most cases, with an average time from the onset of symptoms of four months. In addition to that clinical characteristics related to SLE were variable, along with certain common characteristics such as acanthosis in 60% of patients. Almost all the patients had antibodies against insulin receptors. The insulin doses required by the patients ranged from 450 to 25,000 U daily. Remission was achieved in 80% of the patients with a two-year follow-up. Most patients associated with late-onset SLE, like our patient, achieved metabolic control after immunosuppressive treatment. Conclusion. High insulin resistance in patients with de novo diabetes mellitus (DM) without obesity should be considered as a possible clinical manifestation of an autoimmune disease such as SLE, with a good metabolic response to the immunosuppressive management established.

1. Introduction

Type B insulin resistance syndrome (TBIRS) is a rare autoimmune disease mediated by autoantibodies directed against insulin receptors, leading to hyperglycemia secondary to severe insulin resistance; however, it can lead to hypoglycemia as well [1]. The cases recorded in the literature typically show women of reproductive age, mainly with systemic lupus erythematosus (SLE) in up to 33% [2]. Patients usually present with weight loss, hyperandrogenism, diffuse acanthosis nigricans associated with insulin resistance, hyperadiponectemia, and hypotriglyceridemia. No standardized treatment exists for this syndrome; however, multiple treatment schemes with variable success rates have been described, including spontaneous remission in up to 33% of patients [3]. Mortality rates can be as high as 50% and the cause of death is usually related to hypoglycemia complications [2].

In the present case report, an elderly nonobese patient with de novo diabetes mellitus diagnosis, high insulin requirement since diagnosis, and inadequate metabolic control is described. The systematic workup of differential diagnosis led to the finding of an autoimmune disease which explains the clinical picture of the patient. In addition, an
Type B insulin resistance syndrome (TBIRS) is an extremely rare entity, with unknown prevalence. Only 116 cases have been described in the literature [2, 4]. The first time this disease was described was in 1975 when six patients presented with overt insulin resistance with acanthosis nigricans and high insulin requirements due to a serum-circulating factor which affected insulin binding to its receptor [5]. These patients required up to 100 times more insulin. Extreme requirements from 700 up to 177,500 insulin units per day were registered [6].

Some authors like Willard et al. [1], suggest that the biochemical triad of extremely high levels of fasting insulin, hyperadiponectinemia, and hypotriglyceridemia in patients with acanthosis nigricans and underlying autoimmune disease may be considered as a clinical definition of TBIRS. In addition, other CHARACTERISTICS may lead to TBIRS suspicions, such as slim patients with insulin requirements higher than 3 U/kg/day and persistent hyperglycemia [7].

Three mechanisms have been described for hyperglycemia in this disorder [1]: autoantibodies competing for the insulin receptor binding site, the binding of such autoantibodies leading to receptor degradation, and the agonist/antagonist action of these autoantibodies with a biphasic response (hypo and hyperglycemia).

The biggest TBIRS cohort was obtained in the National Institutes of Health (NIH). In this cohort, 24 patients were followed for 28 years, finding that TBIRS is more frequent in African American women, with an underlying autoimmune disease, and an age between 20 and 68 years, although teenager cases have been described [3]. In these patients, only three of them developed hypoglycemia, and SLE was observed in up to 46% of patients. Most had a BMI less than 30 kg/m² and in those with a BMI lower than 25 kg/m², one third presented with hypoglycemia and two thirds with hyperglycemia, reflecting an insulin resistance profile different to those with obesity. Perioral and perioral acanthosis nigricans were observed in up to 88% of patients; other patients presented with a deeper voice and lower extremity wasting due to overweight. In the autoimmune laboratory, ANA was observed in 83% of patients and hypo-complementemias (C3 predominantly) in 21%. 25% had spontaneous remission and patients treated with glucocorticoids, cyclophosphamide, plasmapheresis, cyclosporine, and azathioprine had a variable response time from five months up to 54 months.

In a recent systematic review [2], 115 TBIRS cases were reported. Most were women (76.5%) with a mean age of 42 years. 50% had normal weight and acanthosis nigricans,

### 3. Case Presentation

A 62-year-old African American female, with a personal history of de novo diabetes mellitus with insulin requirements, two to three months, with no micro or macrovascular complications, treated with high insulin doses (50 U glargine twice a day, and 20 U glulisine three times a day), without achievement of metabolic control. The patient was referred to a fourth-level hospital based on a malignant neoplasm suspicion: weight loss of 20–30 kg in the last two to three months (her weight at the time of evaluation was 100 kg) and absence of metabolic control. The patient mentioned occasional Raynaud’s phenomenon. Periocular and perioral acanthosis nigricans (Figure 2), and a left supraclavicular mobile lymphadenopathy of 1 cm diameter, with no inflammatory changes, were observed in physical examination. The rest of the physical examination was unremarkable. During in-patient stance, glucometer registry was between 350–400 mg/dL, despite receiving glargine insulin 138 U/day and glulisine insulin 44 U three times a day.

In Table 1, the main laboratory findings are registered, including lymphopenia and positive antinuclear antibodies (ANA) that associated with Raynaud’s phenomenon, suggested a late-onset systemic lupus erythematosus (SLE) diagnosis. However, as a malignant neoplasm was suspected, a cervical lymph node biopsy and a bone marrow biopsy were performed, which were unremarkable. The rest of the endocrine imaging tests were normal.

Due to the high insulin requirements, an insulin drip was started and titrated, with the highest dose up to 43 U/kg/day with capillary blood glucometer around 200 mg/dL. An insulin resistance syndrome mediated by autoimmune was suspected based on the clinical presentation—this case, late-onset SLE. Therefore, management with methylprednisolone 250 mg/day for three days and a prednisolone taper starting at 50 mg/day was initiated. Insulin dose was successfully reduced to less than 2 U/kg/day and a bridge with subcutaneous insulin was performed until insulin drip was suspended (Figure 3). Nonetheless, the patient presented catheter-associated bacteremia, which delayed rituximab initiation. Rituximab therapy was finally started, achieving excellent clinical and metabolic results because at discharge, she only required linagliptin for glycemic control without the need for insulin or another hypoglycemic agent. The patient remained on maintenance immunosuppression with prednisolone 5 mg and chloroquine 250 mg daily. Unfortunately, after discharge, she did not return to our institution for reasons related to her health insurance.

### 4. Discussion

Type B insulin resistance syndrome (TBIRS) is an extremely rare entity, with unknown prevalence. Only 116 cases have been described in the literature [2, 4]. The first time this disease was described was in 1975 when six patients presented with overt insulin resistance with acanthosis nigricans and high insulin requirements due to a serum-circulating factor which affected insulin binding to its receptor [5]. These patients required up to 100 times more insulin. Extreme requirements from 700 up to 177,500 insulin units per day were registered [6].

Some authors like Willard et al. [1], suggest that the biochemical triad of extremely high levels of fasting insulin, hyperadiponectinemia, and hypotriglyceridemia in patients with acanthosis nigricans and underlying autoimmune disease may be considered as a clinical definition of TBIRS. In addition, other characteristics may lead to TBIRS suspicions, such as slim patients with insulin requirements higher than 3 U/kg/day and persistent hyperglycemia [7].

Three mechanisms have been described for hyperglycemia in this disorder [1]: autoantibodies competing for the insulin receptor binding site, the binding of such autoantibodies leading to receptor degradation, and the agonist/antagonist action of these autoantibodies with a biphasic response (hypo and hyperglycemia).

The biggest TBIRS cohort was obtained in the National Institutes of Health (NIH). In this cohort, 24 patients were followed for 28 years, finding that TBIRS is more frequent in African American women, with an underlying autoimmune disease, and an age between 20 and 68 years, although teenager cases have been described [3]. In these patients, only three of them developed hypoglycemia, and SLE was observed in up to 46% of patients. Most had a BMI less than 30 kg/m² and in those with a BMI lower than 25 kg/m², one third presented with hypoglycemia and two thirds with hyperglycemia, reflecting an insulin resistance profile different to those with obesity. Perioral and perioral acanthosis nigricans were observed in up to 88% of patients; other patients presented with a deeper voice and lower extremity wasting due to overweight. In the autoimmune laboratory, ANA was observed in 83% of patients and hypo-complementemias (C3 predominantly) in 21%. 25% had spontaneous remission and patients treated with glucocorticoids, cyclophosphamide, plasmapheresis, cyclosporine, and azathioprine had a variable response time from five months up to 54 months.

In a recent systematic review [2], 115 TBIRS cases were reported. Most were women (76.5%) with a mean age of 42 years. 50% had normal weight and acanthosis nigricans,
45% had hyperglycemia, 42.9% had hypoglycemia at any time of the disease course, and diabetic ketoacidosis was observed in only 11.8%. SLE was the main etiology in 33%, as the NIH cohort. In some patients with Hodgkin lymphoma and multiple myeloma, TBIRS was the initial manifestation as a paraneoplastic phenomenon. In relation to laboratory findings, mean HbA1c was 10.8% (5.1–18.7), fasting serum insulin of 1309 μg/dl (0.1–10.584), C peptide of 13.9 ng/mL (0.1–63.0), and triglycerides of 72.8 mg/dL (36–155); autoimmunity laboratory was remarkable for ANA, present in 60%, hypocomplementemia in 20%, and anti-insulin antibodies were ordered in only 36.1% with half being positive.

Out of 115 patients, 83 (70%) achieved disease remission and 20.5% with spontaneous remission. In the first phase, prednisolone was used in 40% of patients (dose of 50–60 mg), cyclophosphamide in 20%, rituximab in 10%, and plasmapheresis in 8–10%. During this phase, remission was achieved in 40% of patients. kQ_heme and daily insulin dose was 1747U/day (54–57,600), which led to admission for intravenous drip titration. Time-to-remission had a mean of four months (0.25–54). No statistically significant
Table 1: Laboratory results during patient’s hospital stay.

| Laboratory tests                                           | Results       | Reference values               |
|------------------------------------------------------------|---------------|--------------------------------|
| Hemoglobin                                                 | 10.1          | 12–15.5 gr/dL                  |
| Leucocytes/neutrophils/lymphocytes                          | 2600/1000/500 | 4000–11,000 × mm³/2000–7000/  |
| Platelets                                                  | 236,000       | 200,000–500,000/mm³            |
| CRP                                                        | 3.01          | 0.01–0.82 mg/dL                |
| ESR                                                        | 14            | 1–20 mm/h                      |
| Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) | 20/18  | 10–40 units/L/7–56 units/L    |
| Total bilirubin/direct bilirubin                           | 0.66/0.22     | 0.1–1.2 mg/dL/c0.3 mg/dL      |
| Alkaline phosphatase/gamma glutamyl transferase (GGT)      | 45/29         | 20–140 U/L/9–48 U/L           |
| Albumin                                                    | 4             | 3.4–5.4 g/dL                   |
| LDH                                                        | 230           | 140–280 U/L                    |
| Ferritin                                                   | 307           | 20–200 ng/mL                   |
| Na⁺/K⁺/Cl⁻/Ca²⁺/Mg                                         | 138/3.8/8.8/2.2 | mEq/L                         |
| Triglycerides                                              | 50            | <150 mg/dL                     |
| PT/INR/PPT                                                 | 10/0.9/24     | 10–12 s/0.9–1.15/25–35 s      |

Autoimmunity laboratory

| Antinuclear antibodies (ANA)                               | 1:2560 speckled | Positive> 1:80                  |
| C₃/C₄                                                      | C₃ 50 mg/dl C₄ 8 mg/dl | C₃ 80–160 mg/dl/C₄ 15 a 52 mg/dL |
| Anti-DNA                                                   | Positive        | Positive >1:10                  |
| Extractable nuclear antigen antibodies (ENA)              | Anti Ro (+)     | Positive >20 units              |
| Antineutrophil cytoplasmatic antibodies (ANCA)            | Negative        | Negative                        |
| Antiphospholipid antibodies                                | Negative        | Negative                        |
| Basal insulin                                              | 25.3           | 18–48 pmol/L                   |
| C peptide                                                  | 30             | 0–4.0 ng/mL                    |
| Anti-insulin antibodies                                    | Positive        | Negative                        |

Figure 3: Blood glucose plot. Improvement after IV methylprednisolone pulse and oral prednisolone therapy.
Table 2: SLE-associated TBIRS patients’ description.

| Gender/age, race | Time- to diabetes diagnosis | Time- to resistance | ANA titer/pattern | Acanthosis nigricans | SLE characteristics | ACRI-AAI | Maximum daily insulin dose | Treatment | Final outcome |
|------------------|----------------------------|---------------------|-------------------|---------------------|---------------------|---------|------------------------|-----------|---------------|
| 1. F, 62 years, African American, Present case | 3 months | 3 months (catabolic symptoms) | 1:2560 speckled | Yes | Raynaud’s phenomenon, Lymphopenia, Hypocomplementemia | AAI | 2400 U daily dose | Pulse steroid + prednisolone | Remission (metabolic control) |
| 2. F, 47 years, Asian. [4] | 3 months | 3 months (catabolic symptoms) | Positive speckled | Yes | Fever, Oral ulcers, Weight loss, Axillary lymphadenopathies, Leukopenia | ACRI | 12,000 U daily dose | Pulse steroid + 20 mg for 4 weeks | 2 years remission |
| 3. F, 60 years, African American. [8] | 1 year (hypoglycemia) | 3 months (catabolic symptoms) | Not reported | Yes | Nephritides, Dermatomyositis, Raynaud’s phenomenon | ACRI | Hypoglycemias with doses of 1.1 U/kg/day | Mycophenolate + prednisolone + immunoglobulin + rituximab + plasmapheresis + Bortezomib + pulse high-dose dexamethasone | Persistent hypoglycemias (12 months) |
| 4. F, 8 years, Latina. [9] | Unknown | 3 months (hypoglycemia) | 1:640 | Yes | Nephritis, Dermatomyositis, Raynaud’s phenomenon | ACRI | Hypoglycemias with no antidiabetic drugs (despite glucocorticoids, glucagon and octreotide) | Methylprednisolone 40 mg/day | Remission (unknown follow-up) |
| 5. F, 39 years, African American. [10] | 6 months (catabolic symptoms) | 1 month (hypoglycemia) | 1:2560 speckled | Yes | Antiphospholipid antibodies | AAI | 1500 U daily dose | Pulse steroid + prednisolone | Remission (12 months follow-up) |
| 6. M, 63 years, Asian. [11] | 4 months (catabolic symptoms) | 4 months (uncontrolled hyperglycemia) | 1:320 | Yes | Nephritis, Cryoglobulinemia | ACRI | 306 U daily | Rituximab + pulse high dose dexamethasone each 4 months for 4 days + maintenance with azathioprine | Remission (unknown follow-up) |
| 7. M, 60 years, Asian. [12] | Unknown | Unknown | 1:2560 speckled | No | Ataxia photosensitivity, Thrombocytopenia, Lymphopenia, Hypocomplementemia | ACRI | Continuous infusion 9 mU/kg/min | Rituximab + prednisolone + cyclosporine | Remission (unknown follow-up)—nephrotic syndrome development |
| 8. M, 44 years, Asian. [13] | 1 year (hyperglycemia) | Unknown (hypoglycemia) | Positive—unknown titers | Yes | Polyaarthralgias, Hypocomplementemia, Hypergammaglobulinemia | ACRI | Hypoglycemias with no antidiabetic drugs | Rituximab | Remission (unknown follow-up) |
| Gender/age, race | Time- to diabetes diagnosis | Time-to resistance | ANA titer/pattern | Acanthosis nigricans | SLE characteristics | ACRI-AAI | Maximum daily insulin dose | Treatment | Final outcome |
|-----------------|-----------------------------|-------------------|-------------------|---------------------|--------------------|----------|--------------------------|-----------|---------------|
| 9. F, 46 years, Asian. [14] | No diagnosis | 3 months | Positive—unknown titers | No | Raynaud’s phenomenon<br>Thrombocytopenia<br>Hypocomplementemia<br>Nephritis | Negative | 600 U daily | Immunoglobulin + cyclophosphamide + leflunomide | Remission (unknown follow-up) |
| 10. F, 38 years, Asian [15] | Unknown | Unknown (hypoglycemias) | Positive—unknown titers | No | Photosensitivity<br>Interstitial lung disease | ACRI | Hypoglycemia with no antidiabetic drugs | Prednisolone 30 mg/day + chloroquine 300 mg/day + azathioprine 50 mg/day | Remission (unknown follow-up) |
| 11. F, 38 years, Caucasian. [16] | Unknown | 2 months (renal failure and catabolic symptoms) | Positive 1:1280 speckled | Yes | Nephritis<br>Malar rash<br>Myalgias<br>Arthralgias | ACRI | 2400 U daily | Mycophenolate + pulse steroids + plasmapheresis + rituximab + IV immunoglobulin | Persistent hypoglycemia with glucose supplement requirement and continuous enteral nutrition |
| 12. F, 50 years, African American. [17] | Unknown | Unknown | Positive | No | Unknown | ACRI | 1300 U daily | 1 rituximab cycle + 3 pulse steroid | Remission (16 months follow-up) |
| 13. M, 62 years, African American. [17] | Unknown | Unknown | Positive | No | Antiphospholipid antibodies | ACRI | 1250 U daily | 2 rituximab cycles + 3 pulse steroid | Remission (12 months follow-up) |
| 14. M, 64 years, Caucasian. [17] | Unknown | Unknown | Positive—unknown titers | No | Raynaud’s phenomenon<br>arthritis<br>Alveolar hemorrhage<br>Lymphadenopathies<br>Pancytopenia with AIHA<br>Hypocomplementemia | ACRI | 1800 U daily | Cyclophosphamide cycles + prednisolone + Cyclosporine + Metformin | Remission (3 months follow-up) |
| 15. M, 59 years, Asian. [18] | No diagnosis | 1 month (catabolic symptoms) | Positive 1:80 speckled | No | Raynaud’s phenomenon<br>arthritis<br>Alveolar hemorrhage<br>Lymphadenopathies<br>Pancytopenia with AIHA<br>Hypocomplementemia | ACRI | 1800 U daily | | Remission (15 months follow-up) |
| Gender/age, race | Time-to diabetes diagnosis | Time-to resistance | ANA titer/pattern | Acanthosis nigricans | SLE characteristics | ACRI-AAI | Maximum daily insulin dose | Treatment | Final outcome |
|------------------|---------------------------|-------------------|------------------|---------------------|--------------------|----------|--------------------------|-----------|--------------|
| 16. M, 37 years, Asian. [19] | Unknown | 3 months (hypoglycemias) | Positive—unknown titers | No | | | | Prednisolone 60 mg/day + chloroquine 250 mg/day + cyclophosphamide 600 mg every 2 weeks for 6 months | Remission (unknown follow-up) |
| 17. F, 50 years, from India. [20] | No diagnosis | Unknown (catabolic symptoms) | Positive 1 : 100 homogeneous | Yes | Oral ulcers Weight loss Fatigue Anemia arthritis Skin lesions | ACRI 2000 U daily | Methylprednisolone pulse + prednisolone + Azathioprine | Remission (unknown follow-up) |
| 18. F, 23 years, Asian. [21] | No diagnosis | Unknown (catabolic symptoms) | Positive 1 : 320 speckled | Yes | Nephritis Hypocomplementemia | ACRI Unknown | Methylprednisolone pulse + prednisolone | Initial remission Death due to P. jiroveci pneumonia |
| 19. F, 13 years, African American. [22] | No diagnosis | 3 months | Unknown | No | Unknown | ACRI 450 U daily rosiglitazone metformin | Prednisolone 60 mg daily | Unknown |
| 20. F, 40 years, African American. [23] | No diagnosis | 1 month (asymptomatic hyperglycemia) | Unknown | Yes | Nephritis | ACRI 4500 U daily | Methylprednisolone pulse + cyclophosphamide | Remission (unknown follow-up) |
| 21. F, 37 years, African American. [24] | No diagnosis | 6 months | Positive—unknown titers | Yes | Arthritis Raynaud’s phenomenon | ACRI 3000 U daily | Methylprednisolone pulse + Prednisolone + 5 plasmapheresis cycles + 6 cyclophosphamide cycles | Remission (11 months follow-up) |
| Gender/age, race | Time- to diabetes diagnosis | Time- to resistance | ANA titer/pattern | Acanthosis nigricans | SLE characteristics | ACRI-AAI | Maximum daily insulin dose | Treatment | Final outcome |
|-----------------|-----------------------------|--------------------|------------------|---------------------|---------------------|---------|--------------------------|-----------|---------------|
| 22. F, 27 years, African American. [25] | No diagnosis | Unknown | 1:640 | Yes | Pericarditis Arthritis | ACRI | 600 U daily | 2 cyclophosphamide cycles + prednisolone + maintenance with mycophenolate mofetil | Prednisolone 30 mg + IFG-1 methylprednisolone pulse + 6 methylprednisolone pulses | Remission (unknown follow-up) |
| 23. F, 50 years, Asian. [26] | Unknown | 1 month | 1:2560 homogeneous | Yes | Hypocomplementemia | ACRI | 1200 U daily | 2 cyclophosphamide cycles | Remission (unknown follow-up) |
| 24. F, 16 years, Latin. [27] | Unknown | 2 months (catabolic symptoms) | 1:1280 | Yes | Nephritis, Pancytopenia, Serositis | ACRI | Unknown | 2 methylprednisolone pulses + Cyclophosphamide + prednisolone 30 mg daily Prednisolone for 3 months (80–40 mg/day) | Remission (unknown follow-up) |
| 25. M, 69 years, Asian. [28] | No diagnosis | 13 months (hypoglycemia) | 1:1280 speckled | Yes | Raynaud’s phenomenon, Hypocomplementemia Nephritis | ACRI | Unknown | 2 methylprednisolone pulses + Cyclophosphamide + prednisolone 30 mg daily Prednisolone for 3 months (80–40 mg/day) | Remission (unknown follow-up) |
| 26. F, 59 years, Caucasian. [29] | No diagnosis | 15 months (catabolic symptoms and hypoglycemia) | Positive speckled (no titers) | No | Hypocomplementemia, Leukopenia | ACRI | Unknown | 2 methylprednisolone pulses + Cyclophosphamide + prednisolone 30 mg daily Prednisolone for 3 months (80–40 mg/day) | Remission (unknown follow-up) |
| 27. F, 24 years, Caucasian. [30] | No diagnosis | 9 months (hypoglycemia) | Positive 1:64 | No | Discoid lupus, Lymphadenopathies Fever Serositis Arthritis, Leukopenia, Lymphopenia, Hypocomplementemia | ACRI | Unknown | 2 methylprednisolone pulses + Cyclophosphamide + prednisolone 30 mg daily Prednisolone for 3 months (80–40 mg/day) | Remission (unknown follow-up) |
| 28. F, 52 years, African American. [31] | No diagnosis | 1 month (hypoglycemia) | Positive 1:2084 homogeneous | No | Arthritis, Alopecia, Hypocomplementemia, Leukopenia | ACRI | Unknown | 2 methylprednisolone pulses + Cyclophosphamide + prednisolone 30 mg daily Prednisolone for 3 months (80–40 mg/day) | Remission (unknown follow-up) |
| Gender/age, race | Time- to diabetes diagnosis | Time- to resistance | ANA titer/pattern | Acanthosis nigricans | SLE characteristics | ACRI-AAI | Maximum daily insulin dose | Treatment | Final outcome |
|-----------------|----------------------------|---------------------|-------------------|---------------------|---------------------|---------|---------------------------|-----------|--------------|
| 29. F, 49 years, African American. [32] | 2 years | 14 months (catabolic symptoms) | Positive 1:160 speckled | Yes | Alopecia | ACRI | 24,000 daily | prednisone | Death (unknown cause) |
| 31. F, 23 years, African American. [32] | Unknown | 9 months (catabolic symptoms) | Positive—unknown titers | Yes | Arthritis | ACRI | 6000 UI daily | Pulse steroids | Death (unknown cause) |
| 32. F, 51 years, African American. [33] | 4 years | 8 months (catabolic symptoms) | Positive 1:160 speckled | Yes | Alopecia | No tested | 25,000 U daily | No drugs | Spontaneous remission (20 months follow-up) |
relationship could be established between negative anti-insulin antibodies and disease remission. The mortality in this systematic review was 15.38%; one out of four patients died due to intractable hypoglycemia.

Thirty-one SLE-associated TBIRS cases have been described (Tables 2 and 3), these patients had hypoglycemia (35%) or catabolic symptoms and hyperglycemia (66%) as the initial symptoms. The time of symptom onset was from one up to 15 months. The most common ANA pattern was speckled (32%). No single SLE sign or symptom was predominant, as the clinical presentation was variable among all patients. Acanthosis nigricans was present in 60% of patients. Predominant antibodies were anti-insulin receptors (97%). 37.5% TBIRS were associated with late-onset SLE. Insulin doses required were between 450–25,000 U/day. Remission was achieved in 80% of patients with a follow-up of two years. 10% of patients did not respond to the therapy, with persistent hypoglycemia. Most late-onset SLE-associated TBIRS required additional immunosuppressant therapy to achieve remission and metabolic control (other than steroids). Nonetheless, in our patient glycemic control was achieved after glucocorticoid therapy. An interesting finding in our patient was that in addition to anti-insulin antibodies, normal C peptide, and fasting insulin, clinical signs of insulin resistance and high insulin requirements, hypotriglyceridemia was observed, which is suggested as another variable to consider for the diagnosis [1].

The treatment includes two main goals: glycemic control, and immunosuppression when it is required. No single protocol is established, and no clinical trial has been performed in this population. The treatment has certain details which must be considered, such as mean insulin requirement which was up to 5600 U/day in the NIH cohort; some patients required up to 30,000 U/day. Concentrated insulin products may improve insulin administration when higher doses are required. U-500 insulin is five times more concentrated than U-100 insulin [34]; therefore, it is considered the cornerstone of therapy in patients with insulin resistance; unfortunately, it is not available in Colombia. In a nine-study meta-analysis, patients with different types of U-100 and U-500 insulin were included: patients treated with U-500 insulin had a higher weight gain of 4.4 kg, but no difference was observed in hypoglycemics [35]. To administer such high insulin doses safely, the patient must be admitted and an intravenous insulin drip must be started. Treatment schemes have been established by academic medical centers and the main therapeutic goal is normal fasting glucose to achieve metabolic control [35, 36].

Immunosuppression is directed to resolve the underlying autoimmune process. Multiple treatment schemes have been used as was observed in the systematic review by Martins et al. [2]. NIH proposed a standardized treatment regime with a combination of rituximab, monthly pulse steroid therapy (dexamethasone 40 mg/day for four days),

| Clinical and demographic characteristics | Mean and frequencies |
|-----------------------------------------|----------------------|
| Race                                    | African American 39%  |
|                                         | Caucasian 16%         |
|                                         | Asian 39%             |
|                                         | Latin 6%              |
| Age                                     | Mean: 43 years        |
|                                         | Range: 8–69 years     |
| Hypoglycemia                            | 35%                  |
| Acanthosis                              | 61%                  |
| Hypocomplementemia                      | 39%                  |
| Late onset lupus (≥50 years)            | 37.5%                |
| ANAs                                    | Speckled: 32%         |
|                                         | Homogeneous: 10%      |
|                                         | No specification/no report: 58% |
| Treatment                               | Steroids: 84%        |
|                                         | Rituximab: 26%       |
|                                         | Azathioprine: 13%    |
|                                         | Mycophenolate: 13%   |
|                                         | Immunoglobulin: 10%  |
|                                         | Cyclophosphamide: 10%|
|                                         | Methotrexate: 10% cyclosporine: 6% |
|                                         | Bortezomib: 3%       |
| Treatment response                      | Spontaneous 3.1%     |
|                                         | Unknown 17.9%        |
|                                         | Remission 80%        |
| Death                                   | 10% (4 patients)     |
|                                         | 2 due to unknown causes|
|                                         | 1 due to P. jirovecii infection |
|                                         | 1 due to motor vehicle accident |
and cyclophosphamid [17]. This scheme was used in a 45-year-old patient with 20 kg unexplained weight loss, disseminated acanthosis nigricans, blood glucose higher than 500 mg/dL, anti-insulin receptor antibodies, and lack of metabolic control despite 600 daily insulin units and no improvement with prednisolone, azathioprine, or plasmapheresis. The patient finally improved after rituximab 750 mg/m² divided into two doses two weeks apart, associated with oral cyclophosphamide 100 mg/day and dexamethasone 40 mg/day for 4 days. Fasting glucose improved down to 80–100 mg/dL, HbA1c was reduced from 11.8% to 6.5%, and perioral, periocular, and periauricular acanthosis nigricans improved as well [37].

5. Conclusion

In conclusion, TBIRS in nonobese patients with de novo diabetes must be considered secondary to an autoimmune disease such as SLE, with a good metabolic response to immunosuppressant management.

Conflicts of Interest

The authors declare that they have no conflicts of interest related to the topic addressed.

References

[1] D. L. Willard, M. Stevenson, and D. Steenkamp, “Type B insulin resistance syndrome,” Current Opinion in Endocrinology Diabetes and Obesity, vol. 23, no. 4, pp. 318–323, 2016.
[2] L. M. Martins, V. O. Fernandes, M. M. D. Carvalho, D. D. Gadilha, P. C. Queiroz, and R. M. Montenegro, “Type B insulin resistance syndrome: a systematic review,” Archives of Endocrinology and Metabolism, vol. 64, no. 4, pp. 337–348, 2020.
[3] E. Arioglu, A. Andewelt, C. Diabo, M. Bell, S. I. Taylor, and P. Gorden, “Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective,” Medicine (Baltimore), vol. 81, no. 2, pp. 87–100, 2002.
[4] G. Rao, Y. V. Chauhan, P. K. Varthakavi, and N. Bhagwat, “A lean lady with acanthosis nigricans and uncontrolled diabetes mellitus,” Cureus, vol. 12, no. 11, Article ID e11330, 2020.
[5] J. S. Flier, C. R. Kahn, J. Roth, and R. S. Bar, “Antibodies that impair insulin receptor binding in an unusual diabetic syndrome with severe insulin resistance,” Science, vol. 190, no. 4209, pp. 63–65, 1975.
[6] C. R. Kahn, J. S. Flier, R. S. Bar et al., “The syndromes of insulin resistance and acanthosis nigricans. Insulinreceptor disorders in man,” New England Journal of Medicine, vol. 294, no. 14, pp. 739–745, 1976.
[7] M. Kotani, N. Tamura, T. Inoue, and I. Tanaka, “A case of type B insulin resistance syndrome treated with low-dose glucocorticoids,” Endocrinology, Diabetes & Metabolism Case Reports, vol. 2019, 2019.
[8] L. Viswanathan and I. Sirisena, “Immunosuppressive therapy in treatment of refractory hypoglycemia in type B insulin resistance: a case report,” Journal of the Endocrine Society, vol. 1, no. 12, pp. 1435–1439, 2017.
[9] K. Shanker, T. Daley, R. Semple, K. Rouser-Stevens, and J. N. Ham, “Intractable hypoglycemia in the setting of autoimmune overlap syndrome,” Pediatrics, vol. 139, no. 6, Article ID e20160866, 2017.
[10] D. Willard, J. Upadhyay, C. Kim, and D. Steenkamp, “Diabetic ketoacidosis without diabetes,” Journal of Clinical Endocrinology and Metabolism, vol. 101, no. 11, pp. 3870–3873, 2016.
[11] Q. Huang, Y. Yan, H. Zhao, and L. Zuo, “A systemic lupus erythematosus patient presenting as type B insulin resistance complicated with cryoglobulinemia,” Lupus, vol. 26, no. 1, pp. 95–97, 2016.
[12] M. Takei, H. Ishii, Y. Kawai et al., “Efficacy of oral glucocorticoid and cyclosporine in a case of rituximab refractory type B insulin resistance syndrome,” Journal of Diabetes Investigation, vol. 6, no. 6, pp. 734–738, 2015.
[13] O. Bourron, M. Caron-Debarle, M. Hie et al., “Type B Insulin-resistance syndrome: a cause of reversible autoimmune hypoglycaemia,” The Lancet, vol. 384, no. 9953, p. 1548, 2014.
[14] S. Zhang, G. Wang, and J. Wang, “Type B insulin resistance syndrome induced by systemic lupus erythematosus and successfully treated with intravenous immunoglobulin: case report and systematic review,” Clinical Rheumatology, vol. 32, no. 1, pp. 181–188, 2013.
[15] S. M. Kang, H. Y. Jin, K. A. Lee, J. H. Park, H. S. Back, and T. S. Park, “Type B insulinresistance syndrome presenting as autoimmune hypoglycemia, associated with systemic lupus erythematosus and interstitial lung disease,” Korean Journal of Internal Medicine (Korean Edition), vol. 28, no. 1, pp. 98–102, 2013.
[16] I. Buhaescu, S. Rhee, M. R. York, M. McDonnell, and P. A. Merkels, “A woman with severe lupus nephritis and difficult to control diabetes mellitus,” Arthritis Care & Research, vol. 63, no. 4, pp. 623–629, 2011.
[17] R. Malek, A. Y. Chong, B. C. Lupsa et al., “Treatment of type B insulin resistance: a novel approach to reduce insulin receptor autoantibodies,” Journal of Clinical Endocrinology and Metabolism, vol. 95, no. 8, pp. 3641–3647, 2010.
[18] S. Y. Kawashiri, A. Kawakami, K. Fujikawa et al., “Type B insulin resistance complicated with systemic lupus erythematosus,” Internal Medicine, vol. 49, no. 5, pp. 487–490, 2010.
[19] Y. Qing, J. G. Zhou, and G. Yuan, “Systemic lupus erythematosus presenting as hypoglycaemia with insulin receptor antibodies and insulin autoantibodies,” Lupus, vol. 18, no. 5, pp. 457–459, 2009.
[20] V. Ostwal and J. Oak, “Type B insulin resistance in a systemic lupus erythematosus patient,” International Journal of Rheumatic Diseases, vol. 12, no. 2, pp. 174–176, 2009.
[21] Y. Nagayama, H. Morita, D. Komukai, S. Watanabe, and A. Yoshimura, “Type B insulin resistance syndrome induced by increased activity of systemic lupus erythematosus in a hemodialysis patient,” Clinical Nephrology, vol. 69, no. 2, pp. 130–134, 2008.
[22] R. K. Semple, N. H. Halberg, K. Burling et al., “Paradoxical elevation of high-molecular weight adiponectin in acquired extreme insulin resistance due to insulin receptor antibodies,” Diabetes, vol. 56, no. 6, pp. 1712–1717, 2007.
[23] S. Bao, C. Root, and S. Jagasia, “Type B insulin resistance syndrome associated with systemic lupus erythematosus,” Endocrine Practice, vol. 13, no. 1, pp. 51–55, 2007.
[24] A. P. Coll, D. Morganstein, D. Jayne, M. A. Soos, S. O’Rahilly, and J. Burke, “Successful treatment of Type B insulin resistance in a patient with otherwise quiescent systemic lupus erythematosus,” Diabetic Medicine, vol. 22, no. 6, pp. 814-815, 2005.
A. Gehi, A. Webb, M. Nolte, and J. Davis, “Treatment of systemic lupus erythematosus-associated type B insulin resistance syndrome with cyclophosphamide and mycophenolate mofetil,” *Arthritis & Rheumatism*, vol. 48, no. 4, pp. 1067–1070, 2003.

H. Yamasaki, Y. Yamaguchi, N. Fujita et al., “Anti-insulin receptor autoantibodies in a patient with type B insulin resistance and fasting hypoglycemia,” *Acta Diabetologica*, vol. 37, no. 4, pp. 189–196, 2000.

J. S. Baird, J. L. Johnson, D. Elliott-Mills, and L. Opas, “Systemic lupus erythematosus with acanthosis nigricans, hyperpigmentation, and insulin receptor antibody,” *Lupus*, vol. 6, no. 3, pp. 275–278, 1997.

E. Ishimura, K. Goto, T. Kawagishi et al., “Combination of glomerulonephritis with diabetic glomerulopathy in a patient with diabetes mellitus due to autoantibody to insulin receptor,” *Nephron*, vol. 66, no. 1, pp. 105–107, 1994.

S. D. Paolo and R. Giorgino, “Insulin resistance and hypoglycemia in a patient with systemic lupus erythematosus: description of antiinsulin receptor antibodies that enhance insulin binding and inhibit insulin action,” *Journal of Clinical Endocrinology and Metabolism*, vol. 73, no. 3, pp. 650–657, 1991.

R. L. Howard, L. K. Beck, and A. Schneebaum, “Systemic lupus erythematosus presenting as hypoglycemia with insulin receptor antibodies,” *Western Journal of Medicine*, vol. 151, no. 3, pp. 324–325, 1989.

D. E. Moller, R. E. Ratner, D. G. Borenstein, and S. I. Taylor, “Autoantibodies to the insulin receptor as a cause of autoimmune hypoglycemia in systemic lupus erythematosus,” *The American Journal of Medicine*, vol. 84, no. 2, pp. 334–338, 1988.

G. C. Tsokos, P. Gorden, T. Antonovych, C. B. Wilson, and J. E. Balow, “Lupus nephritis and other autoimmune features in patients with diabetes mellitus due to autoantibody to insulin receptors,” *Annals of Internal Medicine*, vol. 102, no. 2, pp. 176–181, 1985.

J. S. Flier, R. S. Bar, M. Muggeo, C. R. Kahn, J. Roth, and P. Gorden, “The evolving clinical course of patients with insulin receptor autoantibodies: spontaneous remission or receptor proliferation with hypoglycemia,” *Journal of Clinical Endocrinology and Metabolism*, vol. 47, no. 5, pp. 985–995, 1978.

E. Cochran, C. Musso, and P. Gorden, “The use of U-500 in patients with extreme insulin resistance,” *Diabetes Care*, vol. 28, no. 5, pp. 1240–1244, 2005.

S. Reutrakul, K. Wroblewski, and R. L. Brown, “Clinical use of U-500 regular insulin: review and meta-analysis,” *Journal of Diabetes Science and Technology*, vol. 6, no. 2, pp. 412–420, 2012.

T. J. Church and S. T. Haines, “Treatment approach to patients with severe insulin resistance,” *Clinical Diabetes*, vol. 34, no. 2, pp. 97–104, 2016.

E. D. Manikas, I. Isaac, R. K. Semple et al., “Successful treatment of type B insulin resistance with rituximab,” *Journal of Clinical Endocrinology and Metabolism*, vol. 100, no. 5, pp. 1719–1722, 2015.