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Editorial

Syndromes of autoantibodies to the insulin receptor

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Introduction

Insulin mediates its metabolic and growth effects following binding to the insulin receptor (IR). The IR is a hetero-tetrameric glycoprotein comprises 2 alpha subunits which are extracellular and 2 beta subunits which are transmembrane [1, 2]. These subunits are linked by disulfide bridges. Following insulin binding to the alpha subunit, the beta subunit undergoes tyrosine auto-phosphorylation. This results in the subsequent phosphorylation of insulin receptor substrates (IRS) and other signal transduction pathways [1, 2]. The metabolic effects (glucose uptake, lipid synthesis, glycogen synthesis, etc.) of insulin are mediated via activation of phosphatidylinositide-3-kinase (PI3K) which in turn activates protein kinase B (AKT). The growth promoting effects of protein synthesis and cell proliferation of insulin are mediated by the Ras-Mitogen activated kinase (MAPK) pathway [1, 2].

Most patients with obesity, metabolic syndrome and type 2 diabetes mellitus (T2DM) have some degree of insulin resistance which contribute to the genesis of the disorder [3]. However in severe insulin resistance insulin levels are far greater and usually >200 mU/L [1, 2, 4, 5].

Rare syndromes of severe insulin resistance can result from mutations in the insulin receptor gene (Type A) or auto-antibodies to the insulin receptor (type B) [1, 2, 4, 5]. In 1976, Kahn et al described these 2 distinct syndromes of insulin resistance-Type A and Type B [4, 5]. In type A insulin resistance, the number of receptors is decreased due to mutations in the insulin receptor [1, 2, 4]. Since then, mutations in the IR gene have been identified in other rare syndromes of severe insulin resistance [1, 2]. These include Rabson-Mendenhall syndrome, Donohue syndrome in addition to the originally reported type A syndrome [1, 2]. Most of these patients have missense or nonsense mutations in the IR gene [1].

In this editorial we review the commoner type B syndrome of insulin resistance (TBIRS) and provide criteria for the presumptive diagnosis of TBIRS to facilitate early diagnosis and treatment given the high mortality of this disorder if left untreated and the ushering in of effective immunotherapy.

Pathogenesis and clinical presentation

Type B insulin resistance syndrome (TBIRS) is a rare autoimmune disorder in which polyclonal autoantibodies are produced against the insulin receptor resulting in a range of glucose abnormalities. Most patients with type B insulin resistance present with moderate to severe refractory hyperglycemia that is usually associated with profound glycosuria, polyuria, and weight loss [4-8]. TBIRS is also one of the two major autoimmune causes of hypoglycemia [7, 8]. TBIRS is due to the development of autoantibodies against the insulin receptor which are usually polyclonal and of the immunoglobulin-G class. The autoantibody acts as a partial agonist (insulin-mimetic) at low concentration and can elicit a hypoglycemic response. However at higher titers, it chronically decreases the cellular response to insulin, resulting in refractory insulin resistance and hyperglycemia [4, 6, 7]. In a rat model, Dobbs elegantly recapitulated both the hypoglycemic and hyperglycemic effects of these autoantibodies [9]. At low

Table 1. Diagnosis of Type B syndrome of insulin resistance

Presumptive diagnosis		Definitive diagnosis
Clinical presentation with severe insulin resistance and diabetes or hypoglycemia associated with an auto-immune disease		Demonstration of autoantibodies to insulin receptor by immunoprecipitation assay in the presence of the clinical syndrome
Biochemical Triad	1-Fasting hyperinsulinemia >21.6 mU/L	
	2-Low or normal triglyceride levels <173 mg/dl	
	3-Increased Adiponectin levels compared to assay reference range	

doses in fasting rats, the antibodies induce hypoglycemia within 2-4 hours lasting 8-24 hours whilst chronic administration of high doses of these auto-antibodies to fed rats induced insulin resistance and hyperglycemia. Furthermore, Kasuga et al showed that these antibodies were insulin-mimetic in adipocytes stimulating glucose uptake and oxidation, protein synthesis and inhibition of lipolysis [10].

The exact prevalence of type B insulin resistance syndrome is not known; however, it is quite rare [6-8, 11]. Based on the National Institutes of Health (NIH) series of 34 patients, it is typically reported in middle-aged (between 30 and 50 years) African American females (85%). This is followed by Asians, while Caucasians seem to be less prone to the syndrome. It is rare in males as we reported recently [12].

The most common clinical presentation described in the literature is the development of severe insulin resistance and diabetes with persistent hyperglycemia despite the use of very high doses of insulin, associated with significant weight loss with widespread acanthosis nigricans [4]. Acanthosis nigricans, a rash of thickened skin and hyperpigmentation seen in severe forms of insulin resistance and is present in 92% of individuals in the NIH series with a predilection for the periocular, perioral regions and labial regions in TBIRS [1, 6, 7]. Hyperandrogenism, with high testosterone level, associated with markedly enlarged ovaries on ultrasound were common in female patients [6, 7, 8, 13]. The hypoglycemia which may occur in the fasting or the postprandial state tends to present in patients with a higher BMI than those who present with hyperglycemia [6, 7, 8, 13]. In a recent series from Japan they suggest that TBIRS occurs more commonly in males (62%) who were older with a mean age of 62.3 years and the usual clinical presentation was hypoglycemia (85.7%) [14].

TBIRS is usually associated with an underlying systemic autoimmune disease such as systemic lupus erythematosus (SLE) but has also been reported to occur with other autoimmune diseases including primary biliary cirrhosis, scleroderma, dermatomyositis and Hashimoto's thyroiditis [6-8, 11, 13]. In the NIH series, SLE was present in 41% of their patients with another 24% having 3 of the 4 criteria for SLE [6, 7]. Interestingly, type B insulin resistance has been shown to manifest after the onset of systemic autoimmune disease, especially SLE. TBIRS may also be a paraneoplastic manifestation of conditions such as Hodgkin's disease and multiple myeloma [6-8].

There are no pathognomonic clinical features that allows for the diagnosis of TBIRS. Normal weight individuals (BMI<27 kg/m^2) with or without glucose intolerance who have a fasting insulin concentration >21.6 mU/L (usually >200 mU/L), confirming insulin resistance, is supportive of the diagnosis. In addition, lean insulin-deficient individuals who require more than 3 units/kg/day of exogenous insulin with persistent hyperglycemia should also raise clinical suspicion of TBIR [13].

Diagnosis

Fasting insulin levels are invariably >21.6 mU/L. Willard et al based on the published literature suggested a triad of biochemical features to support a working diagnosis [13]. This triad included fasting hyperinsulinism, low to normal triglyceride levels and elevated adiponectin levels compared to reference ranges. Depicted in **Table 1** are our proposed criteria for the presumptive diagnosis of TBIRS. In **Table 1** we provide practical cut points for all of these 3 measures, comprising the biochemical triad, but need to point out, due to a lack of standardization, each patients' results should be interpreted with the reported reference range of that laboratory for both insulin and adiponectin also

preferably compared with 5-10 normal weight controls with normal glucose and insulin levels. The paradoxical elevation in adiponectin levels, an insulin sensitizer, in TBIRS was reported as mean levels of 43 mg/L versus controls 8.9 mg/L [15, 16]. The hyperadiponectinemia comprises predominantly the high molecular polymers [15, 16]. Semple et al suggested a level >7 mg/L provided a 97% positive predictive value for an insulin receptoropathy but emphasized the issues of assay standardization and lack of a universal reference material for adiponectin be considered. The other important metabolic feature not consistent with most forms of severe insulin resistance such as lipodystrophy is the low to normal triglyceride (TG) levels. In the NIH series mean values were 54 with a range between 29-172 mg/dl and 49 mg/dl range between 25-68 mg/dl in 24 and 34 patients respectively [6, 7].

The definite diagnostic test is demonstration of autoantibodies to the IR by immunoprecipitation [6, 7].

The confirmation of the diagnosis is difficult since the gold standard of detecting autoantibodies by immunoprecipitation is not available generally not even in reference labs. The method used to detect autoantibodies by immunoprecipitation of recombinant human insulin receptors is not commercially available and tedious, and can be performed at few laboratories worldwide, so serological confirmation by this method is not feasible [13]. Some groups have used inhibition of insulin receptor binding or blocking the biological effects of insulin in-vitro by the patient's serum compared to normal serum as demonstration of an inhibitory antibody [6, 7].

We hypothesize that developing a ratio of the product of fasting insulin and adiponectin divided by TG might provide a better discriminant to diagnose this syndrome given the very poor availability and scarcity of the immunoprecipitation assay demonstrating autoantibodies to the insulin receptor. However this can be only undertaken by the NIH group given they have the largest series of well-defined patients.

In the differential diagnosis in those presenting with hypoglycemia, it is necessary to exclude insulinomas, adrenal insufficiency, hypothyroidism and IGF1, IGF2 producing tumors [8, 13].

Management

The goals of therapy for type B insulin resistance are to 1) reverse the hyper-catabolic state, usually with high doses of intravenous insulin, and 2) eliminate the autoantibodies with immunosuppressive therapy.

Patients were treated with regular insulin or concentrated U-500 insulin (once insulin daily requirement exceed 200 units/d) and insulin sensitizers (metformin), targeting reversal of the hyper-catabolic state, and preventing diabetic ketoacidosis rather than aiming at achieving euglycemia [17, 18]. Dose of insulin increased by 50-300% during steroid treatment.

A treatment protocol aimed at antibody production and general immunosuppression, consisting of rituximab, cyclophosphamide, and pulse steroids and azathioprine was developed by the NIH group [17, 18]. To target antibody-producing B lymphocytes, rituximab, an anti-CD20 monoclonal antibody was used to inhibit production of new antibodies. Pulse steroids consisting of dexamethasone 40 mg orally for four days every four weeks were used to suppress the activity of preexisting antibody producing plasma cells [18]. Compared to continuous steroid therapy this ameliorates the exacerbation of hyperglycemia and other side effects of steroids. Adjunctive immunosuppressive drugs were used to bolster the suppression of both B- and T-cell functions that were contributing to the related autoimmune processes [16, 17]. Cyclophosphamide (100 mg/d) was used as a first-line agent. Remission may be defined as amelioration of hyperglycemia, discontinuation of insulin therapy, normalization of hyperinsulinemia and normalization of hyperandrogenemia [17]. After entering remission, the immunosuppressive regimen was changed to maintenance azathioprine therapy (100 mg/d) [16, 17]. If cyclophosphamide or azathioprine could not be tolerated then cyclosporine was used [17].

This combined regimen resulted in a remission rate of 86.4% in 22 patients with TBIRS in a prospective study with no associated mortality [18]. Hypoglycemia is indicative of a worse prognosis for the disease and was found to be the main cause of death in our review [7, 8, 12]. The authors suggest that the continued therapy with azathioprine helped mitigate against the

risk and sequala of hypoglycemia. These findings contrast to the initial NIH series with a reported a mortality as high as 54% [6]. About one-third of patients remit spontaneously and this could account partly for the dramatic results with the immunosuppression cocktail used. The investigators caution about monitoring these patients closely for side effects during immunosuppressant therapy.

Conclusion

The presence of antibodies to the insulin receptors should be considered in any patient with diabetes with severe insulin resistance requiring excessive doses of insulin or less commonly presenting with hypoglycemia, in the setting of an autoimmune disease like SLE, especially in patients of African American descent. Hopefully in the future an assay will be developed by reference labs to allow clinicians to confirm their clinical diagnosis and manage patients appropriately since immunosuppressant therapy based on the NIH experience appears to be very efficacious. These undiagnosed and untreated patients have a very high mortality.

When the immunoprecipitation assay is unavailable it is not unreasonable to use the biochemical triad (**Table 1**) in addition to the classical clinical presentation to initiate therapy and assess clinical responses given the poor outcomes if untreated and the effectiveness of immunotherapy.

Disclosure of conflict of interest

None.

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References

[1] Boucher J, Kleinridders A and Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harb Perspect Biol 2014; 6: a009191.

[2] Angelidi AM, Filippaios A and Mantzoros CS. Severe insulin resistance syndromes. J Clin Invest 2021; 131: e142245.

[3] American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021; 44 Suppl 1: S15-S33.

[4] Kahn CR, Flier JS, Bar RS, Archer JA, Gorden P, Martin MM and Roth J. The syndromes of insulin resistance and acanthosis nigricans. Insulin-receptor disorders in man. N Engl J Med 1976; 294: 739-745.

[5] Flier JS, Kahn CR, Roth J and Bar RS. Antibodies that impair insulin receptor binding in an unusual diabetic syndrome with severe insulin resistance. Science 1975; 190: 63-65.

[6] Arioglu E, Andewelt A, Diablo C, Bell M, Taylor SI and Gorden P. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective. Medicine (Baltimore) 2002; 81: 87-100.

[7] Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK and Gorden P. Autoimmune forms of hypoglycemia. Medicine (Baltimore) 2009; 88: 141-153.

[8] Censi S, Milan C and Betterle C. Insulin autoimmune syndrome: from diagnosis to clinical management. Ann Transl Med 2018; 6: 335.

[9] Dons RF, Havlik R, Taylor SI, Baird KL, Chernick SS and Gorden P. Clinical disorders associated with autoantibodies to the insulin receptor. Simulation by passive transfer of immunoglobulins to rats. J Clin Invest 1983; 72: 1072-80.

[10] Kasuga M, Akanuma Y, Tsushima T, Suzuki K, Kosaka K and Kibata M. Effects of anti-insulin receptor autoantibody on the metabolism of rat adipocytes. J Clin Endocrinol Metab 1978; 47: 66-77.

[11] Martins LM, Fernandes VO, Carvalho MMD, Gadelha DD, Queiroz PC and Montenegro Junior RM. Type B insulin resistance syndrome: a systematic review. Arch Endocrinol Metab 2020; 64: 337-348.

[12] Jialal I and Devaraj S. An African American male patient with rare type B insulin resistance syndrome. Lab Med 2022; 53: 215-217.

[13] Willard DL, Stevenson M and Steenkamp D. Type B insulin resistance syndrome. Curr Opin Endocrinol Diabetes Obes 2016; 23: 318-323.

[14] Hirota Y, Suwanai H, Yamauchi T and Kadowaki T. Clinical features of type B insulin resistance in Japanese patients: case report and survey-based case series study. J Diabetes Res 2020; 2020: 4359787.

[15] Semple RK, Halberg NH, Burling K, Soos MA, Schraw T, Luan J, Cochran EK, Dunger DB, Wareham NJ, Scherer PE, Gorden P and O'Rahilly S. Paradoxical elevation of high-molecular weight adiponectin in acquired extreme insulin resistance due to insulin receptor antibodies. Diabetes 2007; 56: 1712-7.

[16] Semple RK, Cochran EK, Soos MA, Burling KA, Savage DB, Gorden P and O'Rahilly S. Plasma adiponectin as a marker of insulin receptor dysfunction: clinical utility in severe insulin resistance. Diabetes Care 2008; 31: 977-9.

[17] Malek R, Chong AY, Lupsa BC, Lungu AO, Cochran EK, Soos MA, Semple RK, Balow JE and Gorden P. Treatment of type B insulin resistance: a novel approach to reduce insulin receptor autoantibodies. J Clin Endocrinol Metab 2010; 95: 3641-3647.

[18] Klubo-Gwiezdzinska J, Lange M, Cochran E, Semple RK, Gewert C, Brown RJ and Gorden P. Combined immunosuppressive therapy induces remission in patients with severe Type B insulin resistance: a prospective cohort study. Diabetes Care 2018; 41: 2353-2360.