Lipoatrophic Diabetes in an Elderly Woman: Clinical Course and Serum Adipocytokine Concentrations

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Abstract. Generalized lipodystrophy is a rare disorder of adipose tissue, whose etiology remains unknown. Pathophysiology of this disorder is characterized by generalized loss of body fat associated with an infrequent form of diabetes mellitus (lipoatrophic diabetes). Main features of this form of diabetes mellitus are the severe insulin resistance and the absence of ketoacidosis. Lipodystrophy can be congenital or acquired. In the acquired form, metabolic disturbances usually begin in the first years of life and the response to conventional treatment is very poor. Some alterations in serum adipocytokines have been described in this disease. We report the case of a 74-year-old woman with acquired generalized lipodystrophy who presented with low-normal serum concentrations of leptin, low adiponectin and resistin levels, and high serum levels of TNFα. Patient was initially treated with fenofibrate, metformin and high doses of subcutaneous insulin achieving an adequate metabolic control. During this period, serum adipocytokines were periodically measured. We comment on the different etiopathogenic mechanisms and the therapeutic modalities of this rare syndrome.

Key words: Lipoatrophic diabetes, Leptin, Adiponectin, Resistin, TNFα

LIPOATROPHIC DIABETES (LD) is a well known, although highly uncommon, form of diabetes mellitus [1, 2]. LD refers to a group of extremely infrequent disorders of unknown etiology characterized by the association of nonketotic diabetes mellitus with severe insulin resistance and loss of adipose tissue (lipodystrophy) [2–4]. This lipodystrophy may be either partial or generalized. Generalized lipodystrophy (GL) may be congenital (CGL) or acquired (AGL). The congenital form, also called Berardinelli-Seip syndrome, is an autosomal recessive condition in which total lack of both subcutaneous and visceral fat commonly begins at birth [2, 3]. The acquired form, initially reported by Ziegler in 1928 [5] and, subsequently, described in detail by Lawrence in 1946 (Lawrence syndrome) [4], is usually sporadic although some familial cases have been reported [6]. The age of onset of the disease occurs during the childhood, adolescence or early adult life and diabetes usually occurs after the onset of the lipoatrophy [7]. The onset of the disease in the elderly is an exceptional event. It is generally refractory to conservative treatment although it has been recently reported that leptin-replacement therapy may be effective. To date only 36 patients with AGL have been reported [8].

Adipose tissue is currently considered as an hormonally active system which produces several adipocytokines such as leptin, tumor necrosis factor-α (TNFα), interleukin, adiponectin, and resistin. All of them are involved in the control of metabolism. Leptin is considered to be a fundamental signal of satiety to the brain [9]. Overproduction of TNFα by adipose tissue is involved in insulin resistance in obesity [10]. Adiponectin is a recently discovered adipocytokine with antiatherogenic [11] and anti-inflammatory [12] properties. Finally, resistin has been identified as a novel adipose-specific cysteine-rich protein with ca-
pacity to impair insulin sensitivity and glucose tolerance [13]. Severe lipodystrophy caused by deficiency or destruction of adipose cells is characterized by low leptin and adiponectin levels [14–16]. The effect of the absence of adipose tissue in AGL on serum concentrations of other adipocytokines, such as TNF\(\alpha\) and resistin, is not completely known.

We report the case of a 74-year-old woman with an AGL who developed lipoatrophy and diabetes mellitus during old age. We measured serum concentrations of adipocytokines at diagnosis and during one year of combined therapy with metformin and high doses of insulin. Clinical course, therapeutic aspects and pathogenic implications of these adipocytokines of this rare entity are reviewed.

Case Report

A 74-year-old woman was admitted to the hospital because of poor metabolic control of her diabetes. The patient was in good general state of health until approximately two years earlier, when she developed an ischemic cerebrovascular accident (CVA) of the right cerebral media artery with a slight residual left hemiparesis as sequela. Six months before CVA a diagnosis of type 2 diabetes mellitus was established and oral hypoglycemic agent therapy was started. After 5 months, therapy with oral agents was substituted by subcutaneously administered insulin therapy because of poor metabolic control. She had ingested alcohol in excess for 10 years, but she completely stopped drinking about 8 years before. The patient was known to have colonic diverticulosis, nontoxic multinodular goiter, depressive syndrome, mixed hyperlipemia, lithiasis of the left kidney, and reiterative urinary tract infections. There was no history of hypertension. Her father had suffered from arterial hypertension and died of CVA. The rest of the family history was unremarkable. The patient’s medications comprised lispro insulin analog (196 U/day), alprazolam (2 mg daily), and acetylsalicylic acid (300 mg daily).

The patient presented with asthenia and progressive weight loss, more pronounced in the last three years, associated with adequate food ingestion and appetite (Fig. 1). These symptoms were accompanied by a
continuing worsening of her metabolic control (HbA1c values of 9–10.5%), in spite of high doses of subcutaneous insulin (196 U/day of lispro insulin; 4.4 U/kg/day). There was also a persistent elevation of liver enzymes, as well as severe proteinuria (4.1 g/day).

Her temperature was 36°C, pulse 76 bpm, weight 45.5 kg, body mass index 18.5 kg/m², triceps skinfold 5.8 mm, and muscle arm circumference 19.2 cm. The patient was cachectic with a firm skin and a generalized loss of subcutaneous body fat. Head and neck were normal except for a minimal multinodular goiter and a residual left central facial paralysis. Lungs were clear and the heart was normal. Breasts were normal. Abdomen was soft with normal bowel sounds; the liver edge descended 3 cm below the right costal margin, with a vertical span of 9 cm; the spleen was not palpated. No abdominal or pelvic masses were found. No ascitic fluid was present. The lower extremities showed signs of muscular hypertrophy exhibiting prominent superficial veins and muscles (Fig. 2). On neurologic examination there was a residual left hemiparesis.

Biochemical examinations showed glucose 359 mg/dl (75–110), creatinine 0.9 mg/dl (0.5–1.0), cholesterol 229 mg/dl (50–200), triglycerides 1449 mg/dl (50–200), uric acid 2.6 mg/dl (2.4–5.7), aspartate aminotransferase (ASAT) 75 U/l (<32), alanine aminotransferase (ALAT) 128 U/l (<31), gamma-glutamyl transpeptidase (GGTP) 164 U/l (5–36), lactic dehydrogenase (LDH) 323 U/l (240–480), alkaline phosphatase 178 U/l (91–240), total bilirubin 0.1 mg/dl (0.3–1.1), albumin 3.4 g/dl (3.5–5.0), total protein 6.4 g/dl (6.4–8.3), calcium 9.0 mg/dl (8.5–10.4) and circulating free fatty acids 0.9 mmol/l (0.1–0.6). Hematocrit was 37.1%, white-cell count 5.35 × 10⁹/l, platelet count 150 × 10⁹/l, and erythrocyte sedimentation rate 13 mm/hour. Urine gave 2+ test for glucosuria and ketonuria was negative; the sediment contained 10–15 white cells, 3–6 red cells per high-power field. Plasma sodium was 134 mmol/l (135–145) and potassium was 4.2 mmol/l (3.5–5.0). Prothrombin activity was 80% and partial thromboplastin time 42.6 seconds. Glycosylated hemoglobin (HbA1c) was 8.8%. Creatinine clearance was 50 ml/min and the 24 hour quantified proteinuria was 5.2 g. Serum immunoglobulins (IgG 1090 mg/dl [694–1618], IgA 356 mg/dl [68–378], and IgM 154 mg/dl [60–263]) were normal, and the complement components C3 and C4 were 113 mg/dl (88–201) and 14 mg/dl (16–47), respectively. Serologic testing was negative for antimitochondrial antibodies, antinuclear antibodies (ANA), insulin autoantibodies, IgA antigliadin antibodies, IgA antitransglutaminase antibodies, anti-topoisomerase I (anti-Scl-70) antibodies, anti-LKM autoantibodies, rheumatic factor, and cryoglobulins. Tumor markers (carcinoembryonic antigen; CEA), alpha-fetoprotein, chromogranin A, neuron specific enolase (NSE), CA 19.9, and CA 125) were also negative. Infectious serology (tests for human immunodeficiency virus (HIV), hepatitis B and C antibodies) was negative. Serum hormonal study showed C peptide 8.3 ng/ml (0.7–4.0), insulin 145.3 µU/ml (5–25), glucagon 150 pg/ml (59–177), thyrotropin (TSH) 2.1 µU/ml (0.4–5.0), insulin-like growth factor type 1 (IGF 1) 120 ng/ml (61–102), dehydroepiandrosterone sulfate (DHEA-S) <0.1 µg/ml (0.1–3.3), and androstenedione 0.7 ng/ml (0.2–3.1). Baseline serum concentrations of leptin, adiponectin, and resistin were 2.6 ng/ml (1.0–7.8), 1.8 µg/ml (8–62), and 3 ng/ml (5.3–11.4), respectively. On the contrary, serum concentrations of TNFα were markedly elevated [38.1 pg/ml (<20)] (Table 1).

X-ray film of the chest was normal. Electrocardiogram showed a normal rhythm at a rate of 70 bpm, with left electric axis and negative T-waves in V2-V6. Echocardiogram revealed a moderate concentric hypertrophy of the left ventricle, with reduction of the diastolic function. Ultrasonographic examination of the abdomen was normal without signs of portal hypertension. Ultrasonographic examination of pelvis showed an atrophic genital apparatus. CT scan of the abdomen...
revealed lithiasis of the left kidney. Gastroscopy showed a small hiatus hernia with some small antral ulcers, whereas pylorus, duodenal bulb, and second portion of the duodenum were normal. A test for *Helicobacter pylori* was positive. Colonoscopy revealed colon diverticula. Contrast examination of the small intestine was also normal. Funduscopy study of the eye did not show signs of diabetic retinopathy. Biopsy specimen of the gastric mucosa showed chronic active gastritis, whereas biopsy of the small intestine was normal. Liver biopsy revealed a histologic image of cirrhosis with signs of steatohepatitis. Fat excretion in the feces was 15 g (normal <6 g/day).

During her hospitalization, the patient was initially treated with a 2500 kcal diet with dietary supplementation with ω-3 fatty acid-rich fish oil, and intravenous regular insulin therapy with the objective of improving her nutritional status and glycemic control. However, in spite of employing high doses of intravenous insulin (>100 U/day), her blood glucose levels were not controlled and her corporal body weight continued decreasing until 44.2 kg (Fig. 3). For these reasons, the patient was started on a low fat 2000 kcal diet with dietary supplementation of medium-chain triglyceride (MCT) oil, and subcutaneous U-500 regular insulin (Actrapid, human U-500; 500 U/day). At this moment, metformin was prescribed (850 mg/b.i.d.) with the intention to improve insulin sensitivity. Lipid-lowering therapy with fenofibrate (200 mg/day) was temporarily used to control hyperlipemia, and consequently increasing the sensitivity to exogenous insulin. This drug was employed only for a month due to the fact the patient suffered hepatic cirrhosis. With this therapeutic regime preprandial blood glucose levels were adequately controlled (100–160 mg/dl), by means of a significant lower dose of insulin (285 U/day). In these conditions a partial recovery of weight (47.3 kg) was evident after a month of hospitalization.

**Table 1.** Evolution of the clinical and analytical data of the patient

<table>
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Fig. 3. Plasma glucose level 24 hour profiles during the intravenous infusion of 4 different doses of regular insulin. Note the severe insulin resistance of the patient.

**Discussion**

The patient here reported shows the association of a recent onset generalized lack of body fat with nonketotic diabetes mellitus with severe insulin resistance (hyperinsulinism, increase in serum C peptide levels, and high resistance to exogenous insulin administration), hyperlipidemia (hypertriglyceridemia with high serum levels of fatty acids), hepatomegaly (cirrhosis with signs of steatohepatitis with immunologic study and infectious serology negative), nephrotic proteinuria, muscle hypertrophy and hypertrophy of left ventricle.
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without hypertension. All these findings were compatible with the clinical diagnosis of AGL (Lawrence syndrome). AGL is an extremely infrequent syndrome with less than 40 cases reported to date [4, 6, 7, 8, 15, 17–20]. The present case represents an unexpected and exceptional form of clinical presentation of this syndrome due to the age of onset of both lipoatrophy and diabetes.

Different viral infections, thyroid dysfunction, and pregnancy have been implicated in the etiology of AGL [7, 23]. In our patient there were no clear precipitating factors. The possible etiopathogenic role of excessive amount of alcohol ingested during 10 years and/or reiterative bacterial infections is unclear. Although H. pylori infection is associated with an increased production of cytokines such as TNFα, interleukin-1, -6, and -8 that can alter the glycemic control in diabetic patients, TNFα levels were elevated from the diagnosis and they did not modify with appropriate therapy and after that 13C-urea breath test became negative. Several inflammatory and/or autoimmune mechanisms in the pathogenesis of loss of adipose tissue have been proposed [20, 24]. Some patients show the presence of panniculitis, although this finding has not been uniformly found [7, 14, 25]. Other patients have other associated autoimmune disorders [7]. Hubler et al. [20] reported the presence of autoantibodies against adipocyte membranes in one patient. Recently, it has been proposed a new classification of AGL according to possible etiopathogenic mechanisms [8]. Three types of AGL have been distinguished: type 1, AGL with panniculitis; type 2, AGL with accompanying autoimmune disease; and type 3, idiopathic AGL. Our patient did not have any clinical evidence of panniculitis or autoimmune disease. There were no other associated autoimmune clinical diseases, all the serological and immunological investigations were negative. Although we did not determine insulin receptor antibodies and autoantibodies against adipocyte membranes, the absence of other serum autoantibodies makes the possibility of an immune etiology very improbable. Moreover, endocrinological investigations, including thyroid function tests, were normal, except for the serum concentrations of insulin and C peptide, which were elevated, thus indicating a severe insulin resistance. The negative result of the serum tumor markers, as well as the normal morphologic study, excluded the possibility of a paraneoplastic syndrome. These observations led us to consider the present case as a form of type 3, idiopathic AGL with LD.

Serum leptin concentrations reflect the amount of body fat being reduced in patients with AGL [15]. Our patient showed low-normal leptin levels indicating a reduction of body fat content. Adiponectin levels are decreased in some insulin-resistant states, such as obesity, type 2 diabetes, and in patients with lipodystrophies [15, 16, 26]. The present case also showed low adiponectin levels with no changes after metformin therapy. This hypoadiponectinemia might be related to extremely reduced body fat content and the association with severe insulin resistance reported in AGL. Resistin is a recently identified cytokine whose functions have been related to insulin resistance [27]. It has been hypothesized that resistin might represent an adipocyte derived substance which would act as a mediator between obesity and insulin resistance [13]. The patient reported here showed low serum concentrations of resistin at diagnosis indicating that the insulin resistance associated to LD is not mediated by this adipocytokine. Finally, it has been suggested that TNFα could be in relation to metabolic disturbances and weight loss described in generalized lipodystrophy [16, 23]. TNFα induces weight loss in experimental animals by several mechanisms including suppression of food intake, suppression of lipoprotein lipase, and catabolic effects on energy storage tissues [28]. Moreover, TNFα produces insulin resistance probably acting through insulin receptor diminishing insulin signaling into the cell [29]. TNFα appears to play a general role in reducing adipose tissue mass promoting apoptosis of both preadipocytes and mature adipocytes [30]. Lastly, patients with HIV-associated lipodystrophy show high levels of TNFα which are negatively correlated with plasma adiponectin suggesting an inhibitory effect of TNFα on adiponectin levels [16]. Our patient also showed high serum TNFα levels, approximately 2 times over the normal range. The extremely elevated concentrations of TNFα suggest that this cytokine might have played a role not only in the loss of body weight, but also in the reduced concentrations of adiponectin and insulin resistance found in this patient.

Several therapeutic modalities have been investigated in the management of AGL showing different clinical results. The optimal diet for AGL is unknown. In order to improve glycemic control and/or hypertriglyceridemia several diet modifications have been suggested. Among them are dietary fat restriction [7],
dietary supplementation with ω-3 fatty acid-rich fish oil [30, 31] or substitution of long-chain fatty acids with medium chain triglyceride (MCT) oil [32], and calorie restriction [33]. In our patient, initial dietary supplementation with ω-3 fatty acid-rich fish oil associated with a moderate high calorie diet was not effective in improving body weight; however, an isocaloric, low-fat (2000 kcal/day, fat percentage 35%, ~78 g) with medium-chain triglyceride (MCT) oil enriched diet was beneficial to increase body weight and to improve glycemic and lipid profiles. The dietetic supplementation with MCT oil was made with the aim of reducing the fat excretion in the feces for improving her nutritional status.

Severe insulin resistance has been managed with very high doses of insulin and drugs that improve insulin sensitivity, especially metformin [7] and troglitazone [21]. The therapeutic role of the new thiazolidinediones, rosiglitazone and pioglitazone, in AGL is not known. It was recently reported that there are partial beneficial therapeutical effects of lispro insulin analog in this disease. The addition of subcutaneous preprandial administration of lispro insulin analog to metformin and intraperitoneal insulin therapy reduced peritoneal insulin requirements and improved glycemic control [18]. Control of hypertriglyceridemia with lipid-lowering therapy with bezafibrate may improve glucose tolerance in these patients [19]. More recently the beneficial metabolic effects with the use of recombinant human leptin (rh-leptin) have been reported in these patients [35–37]. Control of hypertriglyceridemia with lipid-lowering therapy with bezafibrate may improve glucose tolerance in these patients [19]. More recently the beneficial metabolic effects with the use of recombinant human leptin (rh-leptin) have been reported in these patients [35–37]. The administration of subcutaneous rh-leptin twice a day for four months improved glycemic control and decreased triglyceride levels and liver volume with an adequate tolerance [35, 37]. Moreover, insulin resistance was completely reversed in lipoatrophic mice by the combined therapy of physiological doses of leptin and adiponectin [38].

In our patient the use of lispro insulin analog did not show therapeutical advantages with respect to regular insulin. With the aim of improving lipid profile we initially used fenofibrate for a limited period of time due to the presence of histologically demonstrated hepatic cirrhosis. At the same time, metformin, an anti-hyperglycemic and insulin-sensitizing agent, was initiated to reduce blood glucose levels by means of improving insulin-mediated suppression of hepatic glucose production and enhancing insulin-stimulated glucose disposal in skeletal muscle. This combined therapy (metformin and fenofibrate) associated with high doses of insulin was accompanied by a biochemical and clinical improvement that was evident at the first month of therapy. After observing that both glycemic and lipid profile continued improving only with dietetic measures combined with metformin and insulin therapy, and that this treatment was associated with a progressive reduction in insulin needs, it was decided to avoid the use of fenofibrate again. Since that moment, a progressive reduction in serum triglyceride levels was observed (Table 1). This fact could explain, at least in part, the decrease of the exogenous insulin needs and the improvement of glycemic control, as shown by the progressive reduction of HbA1c levels during one year of follow-up. It is possible that after the initial control of hypertriglyceridemia induced by fenofibrate and, thereafter, the improvement of insulin resistance, the long term effect of metformin would contribute to improve the insulin sensitivity and the metabolic control of the patient. In summary, this case suggests that low adiponectin and high TNFα serum levels might act in the pathogenesis of the insulin resistance of the LD in AGL. Moreover, combined therapy with fenofibrate, metformin, and high doses of regular insulin may be a useful therapeutic tool in some cases of this disorder.

References


