Dysregulation of growth hormone in acquired generalized lipodystrophy

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Lipodystrophies are a group of rare disorders characterized by a variable loss of adipose tissue and associated with metabolic disorders in different combinations.[1] Lipodystrophies are classified as inherited or acquired, both of which could be generalized or partial. The acquired generalized form is characterized by loss of fat, which begins in childhood or adolescence and occurs over months or years.[1] The metabolic abnormalities described in lipodystrophies include insulin resistance, diabetes mellitus (DM), dyslipidemia in the form of low high density lipoprotein (HDL) and hypertriglyceridemia, accelerated growth in children, increased metabolic rate, fatty liver and pseudoacromegaly.[1,2] Various abnormalities of the hypothalamic-pituitary axis, mostly related to growth hormone (GH), have been reported in the literature. These abnormalities range from abnormally high levels with no response to suppression to normal low levels with no response to stimulation.[2,3] It was suggested that the excess GH secretion could cause some of the clinical features of lipodystrophy.[4] We report here a case of acquired generalized lipodystrophy (AGL) in which the initial elevated GH levels have actually reverted to normal following standard treatment of the associated insulin resistance, DM and hypertriglyceridemia. This suggests the possible reverse cause-effect relationship between the high levels of GH and some of the metabolic abnormalities observed in lipodystrophy.

A 37-year-old female patient was referred to our center with new onset DM not controlled with a recently started sulfonylurea. She was noted by the referring physician to have a goiter and hepatomegaly. On evaluation, a history of hirsutism, menstrual irregularity and hypertension was found to have been present for 18 years, at which time the patient presented once to our center then lost follow-up. In the interim, the patient got married and had 5 successful pregnancies but in 3 of them she had gestational diabetes. Her recent physical examination showed a hirsute, muscular female with prominent veins and generalized loss of subcutaneous tissue involving all the body but sparing the face. She had coarse facial features and a diffusely enlarged goiter, but was clinically euthyroid. There was no acanthosis nigricans. She had hepatomegaly. Complete blood count, liver function tests, kidney function tests and thyroid function tests were all normal. Her DM was poorly controlled with fasting blood sugar (FBS) readings in the range of 235-336mg/dl and HbA1c of 7.8%. She had a total cholesterol level of 220mg/dl and triglyceride (TG) level of 905mg/dl. Thyroid ultrasound showed a multinodular goiter. Tests for antithyroid antibodies were negative. Abdominal computed tomography scan showed hepatomegaly with features of fatty liver. Liver biopsy confirmed severe fatty infiltration with chronic hepatitis. Viral and autoimmune hepatitis were ruled out by negative serology work up, and no history of hepatotoxic drug intake could be elicited. Dual x-ray absorptiometer scan carried out for body fat assessment showed decreased total body fat. Pituitary-hypothalamic magnetic resonance imaging was normal, and pituitary dynamic studies were normal with the exception of the elevated basal GH level of 73ng/ml, which increased with insulin-induced hypoglycemia to 122ng/ml at 30 minutes, and which was not suppressible by oral glucose suppression test. The patient was treated for her DM, hypertriglyceridemia and fatty liver with 160 units of subcutaneous insulin daily in 3 divided doses, 1gm of metformin twice daily and 600mg of gemfibrozil twice daily. Three months later, her FBS readings were in the range of 144-180mgm/dl; her HgbA1c was 7.3% and her TG level dropped to 428mgm/dl. GH studies were repeated and showed basal GH level of 4.09ng/ml, insulin-induced stimulated level of 9.56ng/ml at 30 minutes and a normally suppressed level of 0.94ng/ml after oral glucose loading test.

The relationship between lipodystrophy and dysregulated GH axis has many facets. Boucher et al[3] described elevated GH, which is resistant to suppression by oral glucose in some of their cases. The presence of acromegaloid features points to the idea that excessive GH secretion is responsible for some of the physical manifestations of lipodystrophy syndromes.[4] However, this does not explain the whole picture, as many patients with lipodystrophy do not have GH elevation. Furthermore, acromegaly is not associated with lipodystrophy. Other suggestions to explain the acromegaloid features in lipodystrophy include increased ratio of insulin-like growth factor 1 (IGF-1) to its binding protein, which allows a relatively unopposed effect of IGF-1 on its

receptor.[5] Another plausible explanation is that hyperinsulinemia related to insulin resistance with preserved sensitivity in some tissues allows the development of the acromegaloid features.[6] The amount and distribution of fat in the body appears to influence GH levels. For example, obese people with or without diabetes, especially those with central obesity are noted to have a low level of GH, while patients with anorexia nervosa have high GH levels and notably low leptin level.[7] Visceral fat loss, with subsequent low leptin levels, is a part of the generalized loss of the body fat noted in AGL, which may partially explain the elevated GH level noted in some of those patients. Leptin replacement in patients with lipodystrophy resulted in improvement of many of the endocrine and metabolic disturbances.[8] High GH levels were noted in uncontrolled DM type-1 patients without lipodystrophy, which was attributed to peripheral GH resistance in the liver and central hypersensitivity at the level of the hypothalamus.[9] Some of these effects maybe present in type 2 diabetes but blunted mainly due to the effect of concomitant obesity.[10] It may be difficult to ascertain whether the mechanisms causing GH elevation in lipodystrophy are unique or they are the same ones operating in uncontrolled diabetes and loss of the visceral fat and its GH-suppressing leptin. The normalization of the GH dynamics in our patient coincided with the improved control of her diabetes.

In conclusion, we can say that the control of associated DM, and hypertriglyceridemia contributes at least in a major way to the reversal of the GH axis dysregulation in some patients with lipodystrophy, and could potentially ameliorate some of their acromegaloid features. Further studies will be needed to confirm such a hypothesis and to delineate the role of leptin and other adipocyte-secreted hormones on GH regulation in lipodystrophic patients.

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