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Effect of Depot Medroxyprogesterone Acetate on Glucose Tolerance in Generalized Lipodystrophy

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Abstract

BACKGROUND—Lipodystrophy is a rare condition causing severe insulin resistance and frank diabetes. Depot medroxyprogesterone acetate (DMPA), a commonly used contraceptive, may worsen glucose tolerance in diabetics and those with lipodystrophy.

CASE—A young woman with generalized lipodystrophy, who previously required greater than 1,000 units of insulin daily, had a normal hemoglobin A1c on leptin and metformin only. After an injection of DMPA, she developed severe hyperglycemia. Her levels returned to near normal only with extremely high doses of insulin (up to 1,700 units/d) and increased doses of leptin and metformin.

CONCLUSION—Progestin-only contraceptives may detrimentally affect glucose tolerance, particularly in patients with lipodystrophy, a cause of severe insulin resistance and leptin deficiency. One DMPA injection appeared to profoundly alter glucose metabolism in this patient with frank diabetes resulting from lipodystrophy. The effect of progestin-only contraceptives on glucose tolerance should be monitored closely in any diabetic patient.

Lipodystrophy is a rare disorder characterized by differential loss of adipose tissue. It can be either generalized, with loss of fat throughout the body, or partial, with loss of fat in specific areas. Associated features include severe insulin resistance leading to diabetes, acanthosis nigricans, dyslipidemia, steato-hepatitis, and features of polycystic ovary syndrome in women.¹ Leptin replacement is a recent experimental therapy for patients with lipodystrophy that appears to improve many of the features of this disorder.²

The effectiveness and metabolic impact of different contraceptive options in patients with lipodystrophy are unknown. Because depot medroxyprogesterone acetate (DMPA) is highly lipid-soluble, its metabolism might be significantly affected by lack of adipose tissue in patients with lipodystrophy. Progestin-only contraceptives have long been proposed to have detrimental effects on glucose tolerance in diabetics. In this case, we present the onset of

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worsening hyperglycemia after DMPA use in a patient with severe diabetes arising from lipodystrophy. Our review of the effects of progesterone on insulin sensitivity prompts us to propose close monitoring for changes in glucose metabolism in women with frank diabetes who start progestin-only contraceptives.

CASE

We present a woman with generalized lipodystrophy. At birth, she was noted to have hepatomegaly and thin limbs. She progressed through puberty and at age 11 began menstruating. After three normal cycles, she became amenorrheic for 2 years. At age 12, elevated glucose and serum triglycerides were noted, and she was diagnosed with lipodystrophy and was started on insulin therapy. Her amenorrhea was treated with combination oral contraceptives, which produced regular withdrawal bleeds.

In 2003, on specialty referral, she had extremely high serum triglyceride levels (5,000 mg/dL) and an hemoglobin A1c of 13.7%, despite thousands of units of insulin daily. Because she was leptin deficient, she started leptin-replacement therapy. Over a 3-year treatment period, her serum triglycerides and glucose lowered to the normal range, and she was tapered off all insulin. She remained on metformin 500 mg twice daily and 1.4 mL leptin once daily with a hemoglobin A1c of 5.6% in January 2006.

In mid-June of 2006, when the patient had breakthrough bleeding on a combination oral contraceptive pill, she was given an intramuscular injection of 150 mg DMPA. In the following weeks, her glucose levels rose to 400 mg/dL. Her metformin dose was doubled, and leptin dosing was increased from 1.4 to 2.0 mL. Despite these adjustments, her glucose remained uncontrolled. On admission in August, random blood glucose level was 333 mg/dL, hemoglobin A1c 12.9%, and triglycerides 704 mg/dL. Insulin was increased to 600 units with breakfast, 600 units with lunch, and 500 units with dinner. With these changes and continued close monitoring, glucose levels began to improve (Table 1).

Medroxyprogesterone acetate (MPA) levels were measured in serum by radioimmunoassay using a technique described by Hiroi et al³ and confirmed by Ortiz in 1977.⁴

Medroxyprogesterone acetate levels during hospitalization revealed a high of 449 pg/mL 59 days after injection and declining to 73 pg/mL 77 days after injection (Fig. 1).

COMMENT

Lipodystrophy is a clinically heterogeneous disorder. Congenital, generalized lipodystrophy, also known as Berardinelli-Seip syndrome, has an estimated incidence of one in 10 million.¹ A nearly complete absence of adipose tissue in a neonate can lead to its early identification. Acquired generalized lipodystrophy is much more common and is characterized by a loss of adipose tissue in the face, arms, and legs and excess fat deposition in the neck and upper back. Notably, this occurs in approximately 40% of human immunodeficiency virus (HIV) patients treated with protease inhibitors for more than 1 year. Lipodystrophy patients are often leptin deficient, and replacement can rectify many metabolic abnormalities.² In our patient, leptin replacement allowed her to wean completely from her previous high doses of insulin, using only metformin and leptin for maintenance.

Studies in the mid-1970s revealed that MPA levels reach peak plasma concentrations 3 weeks after injection of DMPA, remain relatively stable for 2–3 months, and then decline exponentially until undetectable by 4–7 months. Persistent serum levels are likely due to protracted release of the drug from its storage in body fat.⁴ Unlike MPA levels reported in normal women, our patient appeared to have a rapid decline, such that at 2 months after

injection, MPA levels were 50% lower than expected (Fig. 1). Two weeks later, her levels had fallen to those normally seen 5–6 months after injection.

Patients with lipodystrophy and little body fat may be unable to store DMPA. This likely resulted in increased initial serum levels and rapid decline to undetectable levels. Higher initial levels of MPA may worsen the insulin resistance and could have, in this woman with lipodystrophy, contributed to her severe hyperglycemia. Potentially, this initial insult was very difficult to overcome in an already taxed system, leading to the prolonged effects that required this patient's hospitalization. Additionally, after such an insult, the low MPA levels that lingered may have continued to have a metabolic effect.

Hormonal contraception is an attractive option to manage anovulation and amenorrhea in women. Although there is no consensus regarding the use of progestin-only contraceptives in diabetics, the physician prescribing information for DMPA notes that “a decrease in glucose tolerance has been observed ... diabetic patients should be carefully observed while receiving such therapy” (Pharmacia, Depo-Provera Contraceptive Injection [package insert data], 2006). Epidemiologic studies have demonstrated an association between DMPA and increased risk of future diabetes in high-risk populations. One metabolic study of eight patients with frank diabetes within 1–3 months after DMPA demonstrated increasing glucose levels during oral glucose tolerance test. The authors hypothesized that these patients' β cells were unable to respond in this setting.⁵ Based upon these studies as well as our current data, it seems reasonable that diabetic or insulin-resistant patients be counseled effectively regarding the potential effects of a progestin-only contraceptive before initiation. Additionally, their glucose tolerance should be monitored closely during therapy.

How high progesterone levels impair insulin sensitivity at a molecular level is controversial. Ordonez et al⁶ found that high levels of progesterone appear to worsen insulin sensitivity in ovariectomized, streptozocin-induced diabetic rats. Perhaps reduced tyrosine phosphorylation of the insulin receptor substrates by stimulation of serine/threonine kinases and/or tyrosine phosphatases plays a role.⁷ Interestingly, leptin also may impact glucose homeostasis, independent of its effects upon adiposity, by directly regulating some metabolic pathways. Signals mediated via unidentified tyrosine phosphorylation sites on the leptin receptor include the tyrosine phosphorylation of insulin receptor substrate proteins.⁸ If there is a mechanism of action for progesterone to affect insulin resistance, it may act via two different sites. Although most physicians will rarely treat a patient with lipodystrophy, this case illustrates the potentially important effects of progestin-only contraceptives in a common patient population, those with severe insulin resistance or frank diabetes.

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Fig. 1. Medroxyprogesterone acetate (MPA) levels after depot medroxyprogesterone acetate injection. Case, *dashed line*; normal, *solid line*.
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Table 1

Laboratory Parameters and Pharmacologic Management From Before Depot Medroxyprogesterone Acetate Injection to 10.5 Weeks After Injection

	Baseline (January 2006)	Post-DMPA (8 wk)	Post-DMPA (10.5 wk)
Fasting glucose (mg/dL)	100	310	101
Serum insulin (units/mL)	43.6	13.4	NM
Hemoglobin A1c (%)	5.6	12.9	NM
Triglycerides (mg/dL)	217	704	167
Leptin dose (mL BID)	0.7 (3.5 mg)	1 (5 mg)	1.4 (7 mg)
Metformin dose (mg)	1,000	2,000	2,000
Insulin dose (units)	None	1,700	350

DMPA, depot medroxyprogesterone acetate; NM, not measured; BID, twice a day.