Leptin, Adiponectin, and Soluble Delta-Like 1 Homolog (sDlk1) Levels During Pregnancy in a Patient with Familial Partial Lipodystrophy

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Abstract

Background: Lipodystrophy is characterized by decreased and dysfunctional adipose tissue, severe insulin resistance, and decreased fertility. Patients with lipodystrophy lack adipokines, including leptin and adiponectin.

Case: A woman with familial partial lipodystrophy and poorly controlled diabetes mellitus became spontaneously pregnant. At baseline, serum leptin and adiponectin levels were low. During pregnancy, adiponectin tended to decrease further while there was a substantial increase in leptin and sDlk1; values returned to baseline after delivery. The pregnancy was uneventful, the blood sugar well controlled. A healthy girl was born.

Conclusion: Blood sugar control was excellent during pregnancy. Apart from improved monitoring and intrinsic motivation, placental (leptin) and fetal (sDlk1) hormones may have had a beneficial impact on maternal metabolism.

Keywords: Familial lipodystrophy; Pregnancy; Leptin; Adiponectin; sDlk1

Introduction

Lipodystrophy is a rare, heterogeneous disease characterized by body fat loss and abnormal accumulation of subcutaneous fat tissue at other body sites. Fat loss may be partial or complete, and the disease can be acquired or congenital. The extent of fat loss correlates with the severity of metabolic abnormalities (insulin resistance, diabetes mellitus, dyslipidemia, liver steatosis and acanthosis nigricans).

Inherited Forms of Familial Partial Lipodystrophy (FPLD) include the Dunnigan variety (FPLD2), an autosomal dominant disease with a mutation of the LMNA gene [1]. Patients with FPLD2 are born with normal fat distribution, but after the onset of puberty, the subcutaneous fat tissue of extremities and trunk gradually disappears [2]. Many patients, especially women, gain fat in the face, neck and intraabdominally, reminiscent of a cushingoid appearance [3]. These patients often have diabetes mellitus and hypertriglyceridemia. Affected women with lipodystrophy and LMNA mutations have a higher prevalence of PCOS, hyperandrogenism, infertility, gestational diabetes and obstetric complications as compared to the normal population [4,5]. Reduced and dysfunctional fat mass thus appears to cause not only insulin resistance but also reduced fecundity. Patients lack leptin, and replacement therapy with leptin improves not only insulin resistance and glycemic control but also fertility.

Our patient with FPLD, most likely FPLD2, became spontaneously pregnant. We assisted her with glycemic control, and measured serum levels of leptin, adiponectin and soluble Delta-Like Homolog (sDlk1). Excellent glucose control was achieved during pregnancy, and the outcome was favorable.

Case Presentation

A 31-year-old female patient was referred to us for better management of difficult-to-control hypertension for one year and newly diagnosed diabetes mellitus of unclear etiology. She took doxazosin 8 mg and metformin 1 g daily; sitagliptin 50 mg and nifedipine 60 mg were added more recently. Family history revealed that the maternal grandfather and the patient’s mother had a muscular body constitution and diabetes mellitus, and so had the mother’s siblings and the patient’s
cousin.

On physical examination, height was 171 cm, weight 78 kg (BMI 26.7 kg/m²), waist circumference 81 cm. Subcutaneous adipose tissue was absent in the arms, legs and truncal areas; skeletal muscles appeared hypertrophic with prominent peripheral veins of the limbs. Acanthosis nigricans was observed on the neck and arm pits. Facial, posterior cervical, suprascapular and supraclavicular fat accumulation created the impression of cushingoid appearance. The patient herself dated the onset of her peculiar fat distribution to puberty. The clinical phenotype was consistent with FPLD2.

The patient had regular menstrual cycles (28 days). Venous plasma glucose was measured by the hexokinase method (Beckman Analyzer; Fullerton, CA, USA), and glycated hemoglobin (HbA₁c) was measured by Human Total Adiponectin ELISA (R&D Systems, Minneapolis, MN 55413 USA), leptin by Human Leptin ELISA (Millipore Corporation, St. Charles, Missouri 63304 USA), and sDlk1 by ELISA (AdipoGen, Liestal, Switzerland) according to the manufacturer’s protocol.

For comparison, we measured adiponectin, leptin and sDlk1 by the same assays in seven healthy non-pregnant women. Their median (range) age was 28 (20 to 35) years, BMI 20.4 (18.3 to 21.0) kg/m²; HbA₁c 5.3 (5.0% to 5.6%); all of them had normal oral glucose tolerance tests. Written informed consent was obtained from these individuals prior to study inclusion as well as from the patient who consented to drawing additional blood tubes for research and she gave written informed consent to the report of her case.

**Results**

Levels of both adiponectin and leptin were low at baseline (before and after pregnancy), consistent with the clinical diagnosis of lipodystrophy. During pregnancy, there was a slight decrease in adiponectin and a marked rise in serum leptin, up into a low-normal range. Moreover, sDlk1 (low normal at baseline) also increased (Table 1, Figure 1). The patient achieved improved blood sugar control during her pregnancy when she became motivated to intensify glucose monitoring and insulin treatment.

**Discussion**

In a case report by Maguire, a young woman with congenital generalized lipodystrophy received leptin; with such treatment, the patient had menarche, became pregnant and delivered a child; the authors discussed that low leptin levels are probably a major factor limiting fertility in these patients [6]. Contrary to this report, our patient with FPLD2 did not have polycystic ovaries. Despite low serum leptin and increased risk for infertility [4], she was obviously fertile and became spontaneously pregnant. To the best of our knowledge, there are no previous reports published on levels of adipokines and sDlk1 before, during and after pregnancy in patients with FPLD.

In patients with lipodystrophy, adiponectin and leptin are both decreased [7,8]. This characteristic adipokine profile was also seen in our case before and after pregnancy, with much lower adiponectin and leptin levels than control females (Table 1).

In healthy subjects, maternal leptin increases during pregnancy, presumably due to endocrine stimulation of maternal adipose tissue, in addition, by secretion of leptin from the placenta. Adiponectin levels decrease, along with an increase in insulin resistance and hyperinsulinemia. In our patient, the increase in leptin during pregnancy was much more pronounced than in healthy pregnant women. The marked rise in maternal serum leptin concentration during pregnancy in our patient appears to be most readily explained by the contribution from the placenta. On the other hand, adiponectin, starting from a low baseline in our patient also decreased during pregnancy as it usually does in healthy pregnant women. In contrast to leptin, adiponectin is expressed and produced only in maternal adipose tissue and not in the placenta.

sDlk1, as opposed to adiponectin and leptin, cannot be considered an adipokine as it is not secreted by mature adipocytes. Highly expressed in preadipocytes, pituitary, adrenals, and in several fetal tissues, it may be related to adipogenesis and changes in fat mass.
and to fetal growth and maternal metabolism during pregnancy. sDlk1 was not particularly low in our patient with FPLD, and the marked increase observed in maternal serum during pregnancy did not appear to be distinct from the increase observed in pregnancy of healthy females, in line with the concept that maternal sDlk1 is dominated by fetal rather than by maternal production and release. After delivery, adiponectin, leptin and sDlk1 returned to the pre-pregnancy baseline levels as described in healthy pregnant women.

We are not aware of previous literature on the course of adipokines during pregnancy in patients with congenital lipodystrophy, or in patients deficient in sDlk1. These factors, whether produced by the mother, the placenta or the fetus, can have an influence on maternal metabolism and fetal outcome.

Outside pregnancy, the low levels of leptin and adiponectin are thought to contribute to extreme insulin resistance and its metabolic complications in patients with lipodystrophy. In animal models of lipodystrophy, replacing leptin or adiponectin reversed insulin resistance.

For the time of her pregnancy, the patient was very compliant, showed up regularly for the check-ups and consistently adhered to intensive insulin therapy. The question arises whether it was mainly the intrinsic motivation through pregnancy that was responsible for better blood sugar control, or whether possibly the placental (leptin) and fetal (sDlk1) hormones had a beneficial impact on maternal metabolism in our patient with FPLD.

Acknowledgment

We thank Valeria Meyer for diabetes counseling and dedicated support of the patient.

References