Lack of Ketosis in Lipoatrophic Diabetes

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SUMMARY

Several metabolic studies were performed on a thirty-year-old Japanese woman with lipoatrophic diabetes. The fasting serum levels of insulin were high, and the insulin response to glucose ingestion was subnormal. The serum growth hormone levels were normal.

Lipolytic and ketonemic stimuli such as starvation and epinephrine injection failed to increase the serum concentrations of nonesterified fatty acids (NEFA) and ketone bodies. The absence of ketonemia was attributable to the lack of substrate delivered from adipose tissue. DIABETES *21*:827-31, July, 1972.

The most characteristic features of lipoatrophic diabetes, first described as a clinical entity by Lawrence,[1,2] include generalized lipoatrophy, insulin-resistant diabetes without ketosis, hyperlipemia, hepatomegaly, and increased basal metabolic rate (BMR) with euthyroidism. Subsequently more than twenty cases have been reported and have included additional features such as increased linear growth, advanced bone age, hirsutism, skin pigmentation, prominence of muscles, and genital hypertrophy.[3,4] These widely diverse manifestations make it difficult to understand the pathophysiology of this disease.

Lawrence believed that lipoatrophy was the primary defect in this condition, with ketosis absent because of the paucity of mobilizable fat.[1] This report describes the clinical and laboratory abnormalities in our patient and provides data on the metabolism of ketone bodies in this patient which support Lawrence's point of view.

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CASE REPORT

The patient (S.N.), an unmarried Japanese woman, was first seen at Osaka University Hospital in 1959, at the age of 23. She had noted lassitude and thirst for about one year and had been very thin for about ten years. Glycosuria and hyperglycemia were found and the patient was hospitalized. She had a normal infancy and childhood. Her father had mild adult-onset diabetes.

Physical examination revealed generalized lipoatrophy and hepatomegaly 3 cm. below the right costal margin. Urinalysis was positive for sugar (40 to 70 gm. per day), protein (2 to 4 gm. per day) and negative for ketone bodies. Liver function tests were normal. Fasting blood sugar was 326 mg./100 ml., total cholesterol 263 mg. per cent, triglycerides 600 mg. per cent and NEFA 0.71 mEq./L. BUN and serum electrolyte levels were normal. The BMR was +44 per cent. She was treated with insulin in dosage to 150 U. per day, but remained unsatisfactory. After returning home, she discontinued insulin and remained nonketotic for the next seven years.

In May, 1966 she was admitted with dehydration, fever, facial edema, and a subcutaneous abscess of left foot. The abdomen was generally distended, and the lower edge of the liver was palpable 7 cm. below the right costal margin. The patellar and Achilles tendon reflexes were absent. The skinfold thickness, measured with skinfold calipers, was 2 mm. at the upper arm (14-16 mm.), 5 mm. at the scapula (10-16 mm.), and 4 mm. at the abdomen (7-8 mm.). (Normal values in nonobese women of the same age are shown in parentheses.) Examination of the eyegrounds revealed diabetic retinopathy.

Twenty-four hour urines before treatment contained from 60 to 90 gm. of glucose and 4 to 5 gm. of protein; ketone bodies were absent. Urinalysis revealed many leukocytes and bacilli and urine culture grew 10^6 colonies per ml. of Escherichia coli. Stool examination was negative for starch or fat droplets. The fasting blood glucose was 434 mg./100 ml. with triglycerides at 540 mg. per cent and total cholesterol at 156 mg. per cent. Serum total CO_2 content was 26 mEq./L. Serum total ketones measured as acetone were 2.4 mg./100 ml. BUN and serum electrolyte levels were normal. Liver function tests (BSP, transaminases, icterus index, thymol turbidity) were normal. The phenolsulfonphthalein test revealed 3 per cent

excretion of injected dye in fifteen minutes. The BMR was +25 per cent and serum PBI was 6.1 μg. per cent. Urinary excretion of 17-OHCS was 5.2 mg. with 17-KS at 1.9 mg. per day. X-ray examinations demonstrated marked decrease of subcutaneous tissue in the extremities. Urological examination showed atonic bladder with pyelonephritis and hydronephrosis. Treatment with insulin, fluids, and antibiotics was started and the insulin dose was gradually raised to 150 U. per day. Urinary glucose diminished and the fasting blood sugar decreased to values in the neighborhood of 200 mg./100 ml. When insulin was discontinued, the fasting blood sugar level rose to 600 mg./100 ml. Ketonemia did not appear either during febrile or afebrile periods.

METHODS

Glucose, 30 gm. per square meter of body surface, was administered orally after an overnight fast and venous blood samples were obtained for the measurements of glucose, NEFA, triglycerides, ketone bodies, and insulin (IRI). During the last ten hours of a twenty-four-hour fast serial blood samples were obtained for the measurements of serum NEFA and ketone levels. Epinephrine (1:1,000), 0.01 mg./kg. body weight, was injected subcutaneously and blood glucose, serum NEFA and ketone bodies were measured. Bovine Regular insulin, 0.1 U./kg. body weight, was administered intravenously and blood samples were obtained for the measurement of growth hormone. The activity of plasma lipoprotein lipase (LPL) was measured after intravenous administration of 10 mg./kg. of dextran sulfate (Kowa Pharmaceutical Company, Ltd., Japan). LPL activity was measured according to the method of Korn with fat emulsion, Fatgen (Dainippon Pharmaceutical Company, Ltd., Japan), as the substrate.[5]

Blood glucose was measured by Hoffman's[6] ferricyanide method by the AutoAnalyzer. Serum NEFA were determined by the method of Novak.[7] Serum ketones were measured by the modification[8] of the Greenberg and Lester method. Triglycerides were measured by the method of Van Handel.[9] Serum insulin levels were measured by the method of Hales and Randle,[10] and growth hormone was measured by a modification of chromatoelectrophoretic radioimmunoassay.[11,12]

RESULTS

Oral glucose loading revealed a sluggish rise of serum insulin (from 48 to 60 U./ml.) with little decrease in serum NEFA (figure 1). Triglyceride levels were slightly decreased and fluctuated. The twenty-four hours of starvation did not raise serum concentrations of either NEFA or ketone bodies in this patient (figure 2). Following epinephrine administration the serum levels

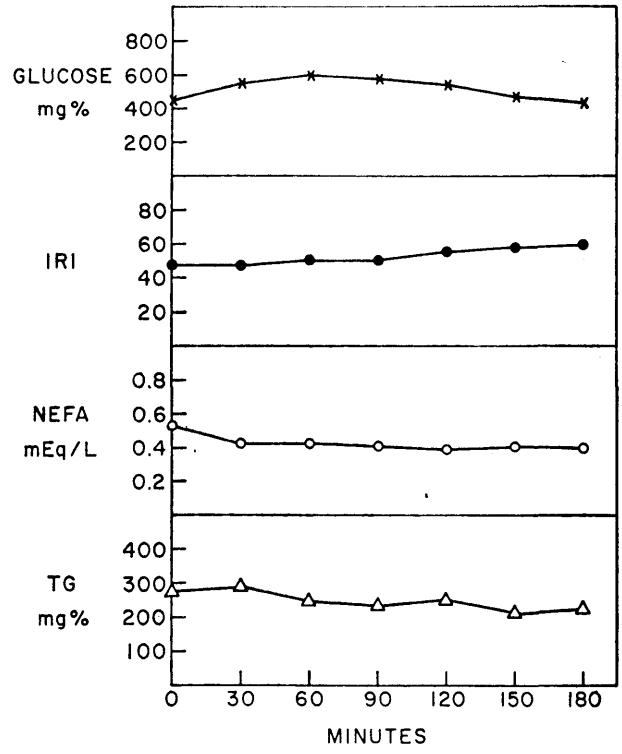

FIG. 1. Changes in blood glucose, IRI, triglyceride (TG), and NEFA during oral glucose tolerance test.

of NEFA and ketone bodies did not change, whereas marked increases of NEFA and ketones were demonstrated in a juvenile diabetic patient and healthy con-

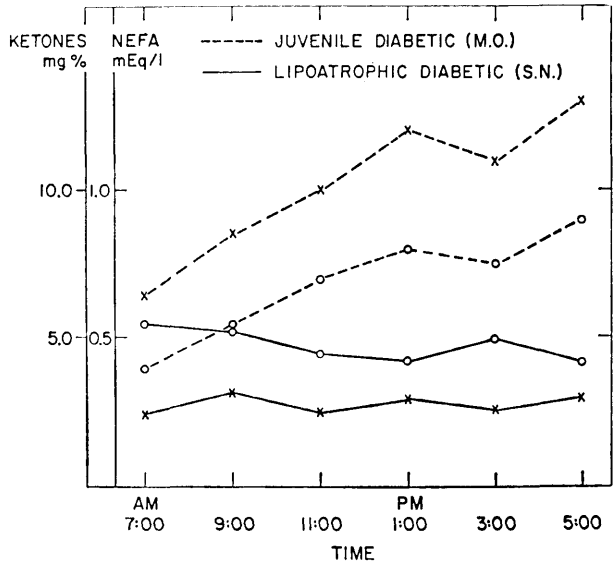

FIG. 2. Effect of starvation on serum NEFA (o-o) and ketone bodies (x-x). The period shown is the last ten hours of a twenty-four-hour fast which started at 5:00 p.m. of the previous night.

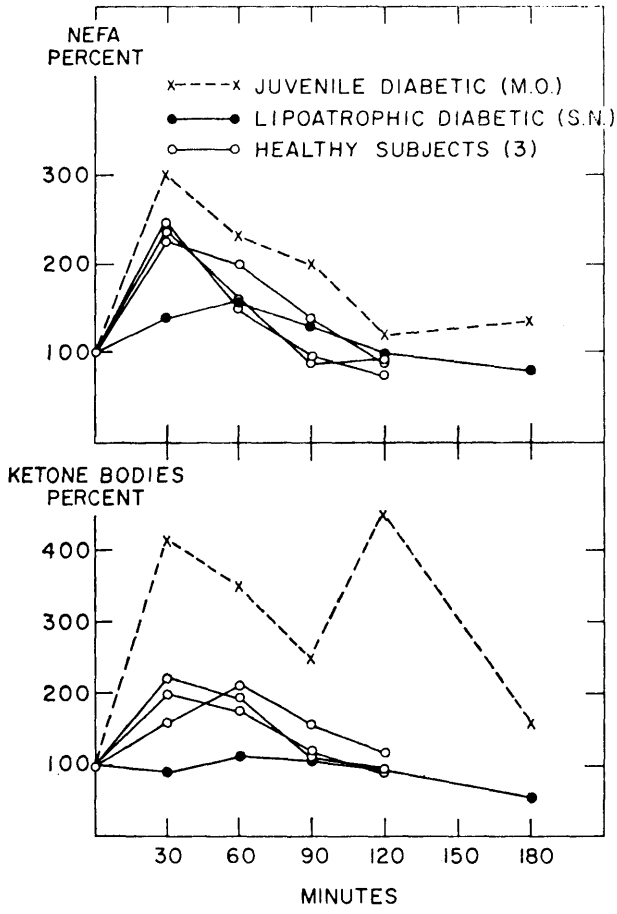

FIG. 3. Per cent change of serum NEFA and ketone bodies during epinephrine test.

trol subjects (figure 3). Blood glucose values during the epinephrine test were 300 mg./100 ml. at fasting, 365 mg./100 ml. at one hour, 420 mg./100 ml. at two hours and 330 mg./100 ml. at three hours, indicating adequate release of glucose from storage in this patient.

The fasting level of serum growth hormone was in the normal range and responded well to intravenous injection of insulin rising from 1.7 ng./ml. to 26.0 ng./ml. (table 1). The increase of plasma LPL activity after dextran sulfate loading was significantly below that recorded in healthy control subjects (figure 4). Insulin antibody in the serum was measured by the method of Berson and Yalow[13] during the second hospitalization and undetected.

DISCUSSION

Most cases of lipoatrophic diabetes have but little tendency to ketosis. Craig and Miller,[14] and Schwartz et al.[15] have described lipoatrophic diabetes without ketonuria despite massive hyperglycemia and glycosuria after omission of insulin therapy. In our patient also ketonuria was absent during hospitalization, even during infection and in the absence of insulin treatment. According to Lawrence[1] the absence of ketosis is simply due to the absence of mobilizable fat. Marcus[16] has suggested that hepatic lipogenesis from acetate increases and thereby prevents an accumulation of ketone bodies. The lipid-mobilizing mechanism in our patient was examined by means of starvation and epinephrine administration. An increase in serum NEFA and ketone bodies after epinephrine injection commonly occurs in normal and diabetic subjects.[17,18] Starvation is also a strong stimulus to increase serum NEFA and ketone bodies. In our patient, however, both ketonemic stimuli failed to provoke an increase in serum NEFA and ketone bodies. Segall and Lloyd,[19] and Senior and Loridan[20] have reported that epinephrine has caused little increase in the concentration of NEFA in their patients with generalized lipodystrophy, although they did not mention ketone bodies. It is unlikely that lipid-mobilizing mechanisms are impaired in lipoatrophic diabetes, since the impairment would lead to accumulation of fat in adipose tissue.[21] Senior and Loridan[20] have suggested that a pathologically small adipose tissue, which is per se either acquired or a genetic disorder, would have a reduced ability to release NEFA. Hence, the absence of ketone bodies after ketonemic stimuli in our patient could be attributed to an insufficient delivery of NEFA from the peripheral adipose tissue to the liver.

Hyperlipemia is also common in lipoatrophic diabetes. Hennes and Shreeve[22] administered acetate 2-C-14 and found that the incorporation of C-14 activity into triglycerides was rather rapid and of the magnitude observed in a young unstable diabetic, but subsequent disappearance of C-14 activity from triglycerides was significantly low. Plasma LPL activity was very low in our patient and Segall and Lloyd[19] also reported the low postheparin lipolytic activity, although Ruvalcaba and Kelley[23] reported the normal lipolytic activity of postheparin plasma in a normolipemic patient with lipoatrophic diabetes. It is conceivable that the depressed activity of the plasma LPL could contribute to hyperlipemia by decreasing the turnover rate of serum lipid. However, it is not known whether this change of LPL activity is one of the basic abnormalities of adipose tisssue or secondary to disturbed glucose metabolism.[5]

Renal disorders such as nephrotic syndrome, proteinuria, and enlarged kidney have been reported in several cases of lipoatrophic diabetes. However, the incidence

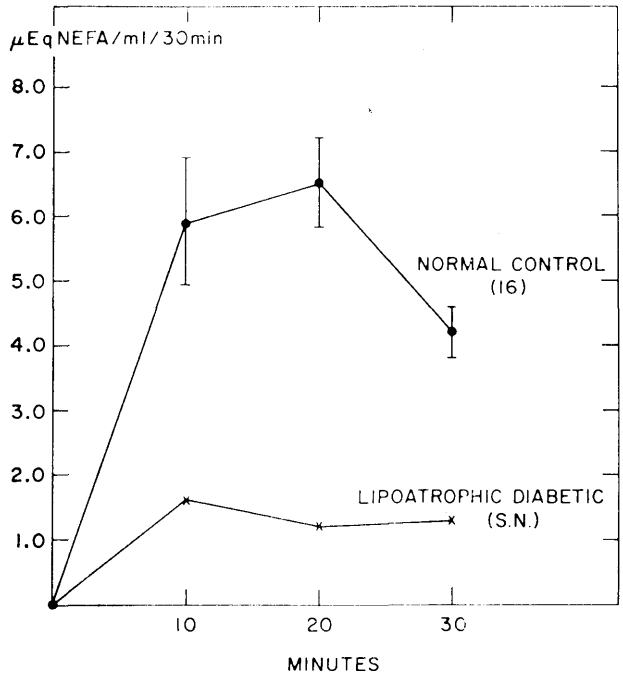

FIG. 4. Plasma lipoprotein lipase activity after dextran sulfate loading. (I: Mean ± SEM)

of chronic complications of diabetes seems quite rare in lipoatrophic diabetes. In 1966, Marcus[16] reported a case with typical chronic complications of diabetes. Our patient has several complications of diabetes, that is, retinopathy, peripheral neuropathy, and a disorder of the autonomic nervous system (manifested as atonic bladder in which cystometry demonstrated the characteristic pattern of autonomic neuropathy).

Adipose tissue has been recognized as a metabolically active organ, where glucose can be converted to fat and stored. Therefore it is reasonable to assume that the absence of adipose tissue could affect lipid and glucose metabolism. In congenital lipoatrophy, which is occasionally combined with some other abnormalities with or without chromosomal anomalies,[24] a congenital absence or functional defect of adipose tissue could be expected. This might not apply to the acquired type of lipoatrophy. Hamwi et al.[25] reported the existence of adipocytes in the subcutaneous tissue, which resembled immature fat cells, although it was not shown that their functions were intact. It is also possible that some factor from outside the adipose tissue, such as growth hormone, increases the mobilization of fat and might prevent the deposition of fat in normal adipose cells. There are no data, however, indicating that growth hormone levels are increased in lipoatrophic diabetes.[25,26] In our patient we

TABLE 1

Plasma growth hormone and blood sugar levels during insulin tolerance test

Time (min.)	Growth hormone (ng./ml.)	Blood glucose (mg./100 ml.)
—30	1.9	466
0	1.7	434
30	18.0	364
45	26.0	360
60	14.0	350
90	5.4	328
120	4.8	308

conclude only that the secretion mechanism of growth hormone examined by insulin injection is demonstrated to be intact.

Louis et al.[27] isolated a polypeptide fraction which exhibited diabetogenic and anti-insulin properties from the urine of four patients with lipoatrophic diabetes. They suggested that this substance could block utilization of glucose in adipose tissue. On the other hand, Chalmers et al.[28,29] reported that fat-mobilizing activity could be detected in normal human urine during fasting and in the fed state in other conditions beside lipoatrophic diabetes. This substance could produce hyperlipemia, ketonemia, fatty liver, transient hypoglycemia, and weight loss in vivo, and release of fatty acid from adipose tissue in vitro in animals. They suggested that this might be a polypeptide of pituitary origin not identical with either growth hormone or corticotrophin. This fat-mobilizing substance extracted by Chalmers et al. has not been shown to be identical with the extracted fraction of Louis et al. Hamwi et al.[25] proposed that the insulin antagonist isolated from urine by Louis et al. could promote rapid hydrolysis of triglyceride to fatty acids and glycerol thereby inhibiting the accumulation of triglyceride in adipose tissue. They suggested that the diverse manifestations in lipoatrophic diabetes could be explained by the existence of a lipid-mobilizing factor. In Chalmers' experiment,[29] however, hypersecretion of a fat-mobilizing substance has been demonstrated in two of four lipoatrophic diabetics, but not in the other two. In a preliminary experiment, using the method of Chalmers et al., lipid-mobilizing activity was also absent from the urine of our patient in the normally fed state.

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