Carbohydrate Metabolism in Primary Growth Hormone Resistance (Laron syndrome) Before and During Insulin-Like Growth Factor-I Treatment

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Among 43 patients with Laron syndrome followed in our clinic, we were able to study the carbohydrate metabolism from infancy into adult age in 30 patients. During infancy, fasting blood glucose levels were in the hypoglycemic range (mean ± SD, 3.5 ± 1.2 mmol/L) and increased at the end of a delayed puberty to 4.6 ± 0.6 mmol/L. Fasting plasma insulin was higher than expected for concomitant glucose levels, and several of the 20 patients who underwent an oral glucose tolerance test (OGTT) had glucose intolerance and relatively high insulin levels. In adult patients, insulinopenia developed and one 38-year-old patient developed non–insulin-dependent diabetes mellitus (NIDDM) with subsequent need for insulin therapy. Continuous insulin-like growth factor-I (IGF-I) treatment of a pubertal patient with glucose intolerance and hyperinsulinemia normalized both responses. In conclusion, long-term IGF-I deficiency leads to insulin resistance, which is reversed by exogenous IGF-I administration.

PRIMARY GROWTH HORMONE (GH) insensitivity or resistance (Laron syndrome [LS])[1] is an autosomal recessive disease resulting from defects in the GH receptor (GHR).[2] These defects can be exon deletions,[3-5] a variety of nonsense, missense, and frameshift mutations, or splice defects.[6,7] Most of these defects occur in the extracellular domain of the GHR[3,5] and are detectable by measuring the level of GH-binding protein,[8] which is identical in structure to this part of the GHR.[9] Recently, LS due to a postreceptor defect has been described,[10] and a transmembrane mutation (exon 8) has also been observed (Silbergeld A, Amselem S, Laron Z, et al, unpublished results, August 1995). The molecular aberrations of the GHR or in postreceptor areas cause a defect in GH signal transduction and thus an inability for insulin-like growth factor-I (IGF-I) synthesis.[11] This, in turn, by a negative feedback mechanism, induces an increased GH-releasing hormone (GHRH) and GH secretion.[12] Clinical features and most biochemical changes of primary IGF-I deficiency are indistinguishable from congenital or early isolated GH deficiency.[13,14] Most of the patients are from either the Mediterranean or Near East areas or are descendants of people originating there.[15,16] The largest cohorts described so far are from Israel[17] and Ecuador,[18] but more and more patients with sporadic mutations are diagnosed now, since clinical IGF-I replacement treatment has become available.[16-19]

Our group had the opportunity to study 43 LS patients and to evaluate most of them from infancy or childhood into adulthood. In addition to being able to establish the natural course of this hormonal deficiency,[20] we were able to study the dynamics of the metabolic impact by chronic IGF-I deprivation.

Among the many biochemical abnormalities resulting from this hormone deficiency starting in utero are those relating directly and indirectly to carbohydrate metabolism.

One of the first characteristics is symptomatic or asymptomatic hypoglycemia.[13,21,22] There are reports of infant and child mortality,[16] most probably related to undiagnosed or untreated hypoglycemia. The parents of one of our patients reported that a sister had died at age 3 in the early 1950s during convulsions and was diagnosed as having viral meningitis.

During years of follow-up study starting in 1958, most of the patients underwent many tests, among which were repeated blood glucose and insulin determinations, oral glucose tolerance tests (OGTTs), and in the early years, insulin tolerance tests.[23]

OBESITY

Untreated patients with LS are already obese at birth[24] and progressively become more and more obese[25] (Figs 1 and 2). They have delayed puberty,[26] but achieve full sexual development and reproduce.[27] The dynamic changes in carbohydrate metabolism over the years will have to be viewed in the perspective of the above developments. Data from the patients was compared with values from established norms in healthy individuals.[28]

BLOOD GLUCOSE

Repeated fasting blood glucose determinations by autoanalyzer in the same patients varied slightly, and the mean levels of LS patients at different ages were always less than the normal values for the respective ages (Table 1, Fig 3). In infancy and early childhood, the difference was significant ($P < .05$). The range of glucose concentrations was wide, and in all age groups patients had hypoglycemia at various times. This was especially true in infancy and early childhood, an age group in which 25% of the samples were less than 2.7 mmol/L (30 mg/dL). During childhood, glucose levels increase, reaching the highest mean values during peak puberty (4.58 ± 0.6 mmol/L, 82.7 ± 11 mg/dL). After puberty, during young adulthood, there was little change.

An additional interesting finding was the changing responsiveness to insulin hypoglycemia between infancy and early puberty (Fig 4). In infancy and early childhood, LS patients present with hypoglycemia nonresponsiveness; between

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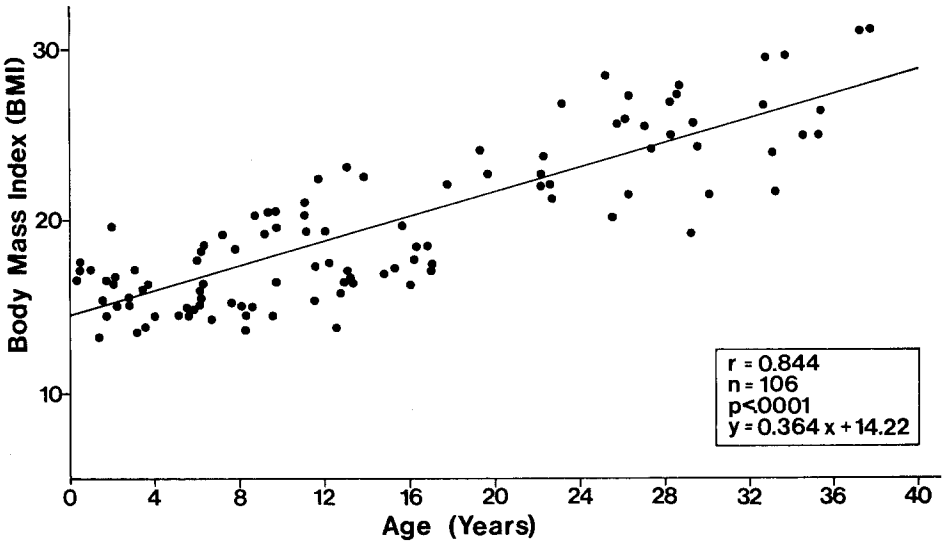

Fig 1. Body mass index with increasing age in patients with LS. It is of note that the patients have thin bones and an underdeveloped muscle mass. (Reprinted with permission.[25])

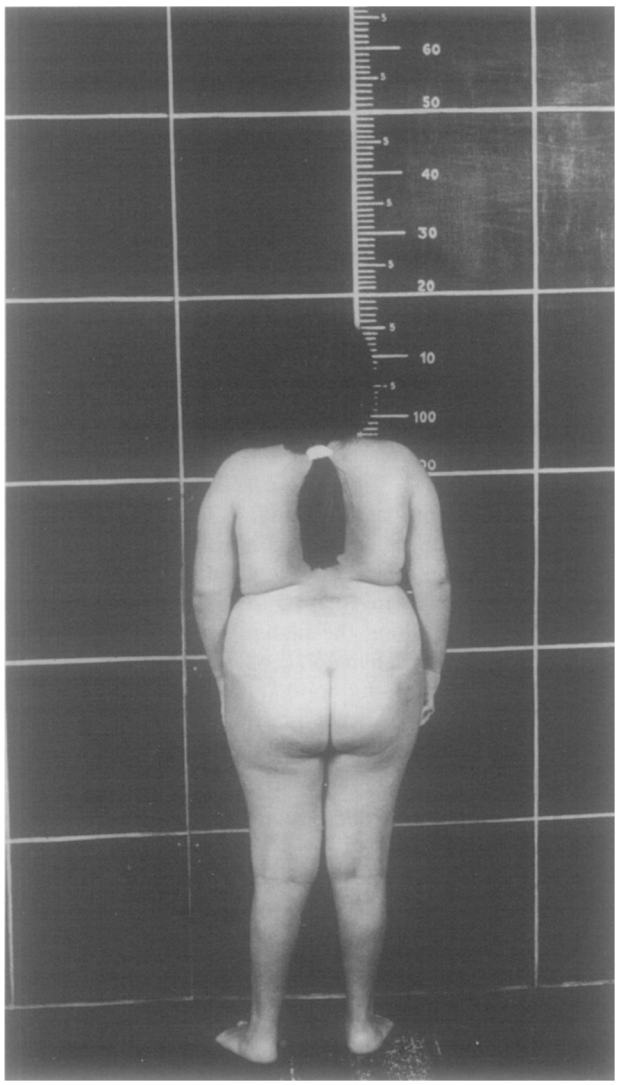

Fig 2. Obesity in a 13-year-old girl with LS.

ages 6 and 8 there is some responsiveness, and during early puberty there is definite hypoglycemia responsiveness. This occurred mainly in girls, whose pubertal stage was more advanced as compared with boys at that age. The normalization by compensatory mechanisms could involve progressive obesity, sex hormones, glucocorticoids, and possibly glucagon (not measured).

PLASMA INSULIN

When comparing overnight fasting insulin levels (Table 2) in different age groups (Fig 5) with the normal values,[28,29] it becomes apparent that in any age group the mean fasting insulin levels are higher than the norms, especially considering the lower-than-normal glucose levels. In the healthy population, female LS patients at puberty have higher insulin values than males ($P < .03$). There were great fluctations in the basal levels of the patients, but the tendency for hyperinsulinemia is evidenced by the maximal levels registered. In infancy (0 to 5 years), 38% of the samples of LS patients are above the upper limit for age (10 μU/mL). Between ages 6 and 10 years, already 63% of the samples are above that level, and during puberty, 76%. In young adult patients, a reversal of this trend starts, with 42% of the samples showing an insulin level less than 5 μU/mL. The trend of relative insulinopenia in adult LS patients was evidenced by a decrease of the insulin to glucose ratio in the overnight-fasted state of over 50% ($P < .006$) between the age groups of 11 to 22 and 23 to 33 years.

Table 1. Fasting Blood Glucose in 30 LS Patients

Age (yr)	No. of Samples	Blood Glucose, mmol/L(mg/dL)	
		Mean ± SD	Range
0-5	51	3.5 ± 1.2 (64.5 ± 22)	0.7-6.8 (13-124)
6-10	51	4.4 ± 0.8 (79.3 ± 14)	2.5-6.0 (45-109)
11-22*	94	4.6 ± 0.6 (83.7 ± 11)	2.6-6.0 (48-110)
23-38	43	4.3 ± 0.6 (78.4 ± 11)	3.1-6.5 (57-118)

*Puberty in LS patients is delayed.[25]

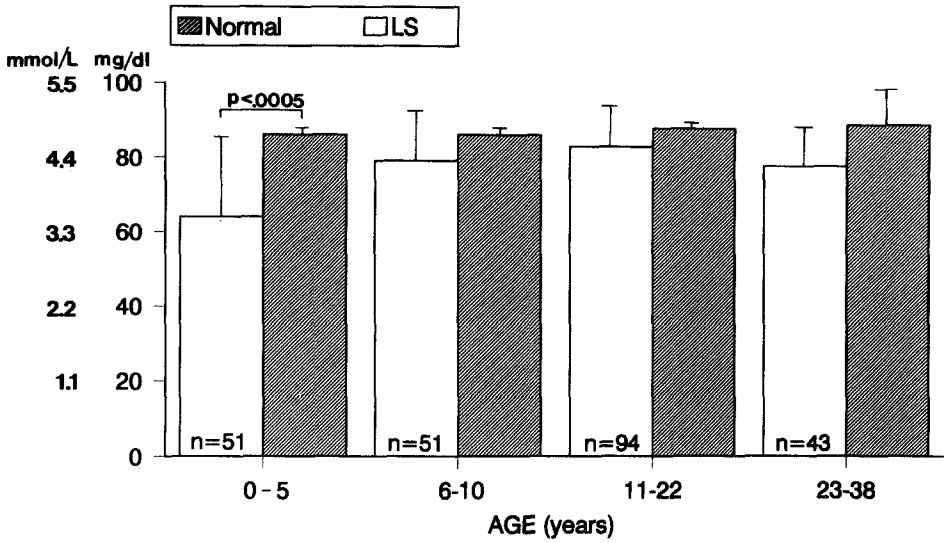

Fig 3. Overnight fasting glucose levels (mean ± SD) in LS patients related to age groups. Normal values from Josefsberg et al.[29]

OGTTs

Additional information on the insulin-glucose relationship and insulin activity in patients with LS, ie, chronic IGF-I deficiency, has been obtained by analyzing glucose and insulin responses to an oral glucose tolerance test ([OGTT] 1.6 g/kg = 45 g/m^2).[27]

Forty-nine OGTTs were performed in 20 patients aged 1 to 33 years. In addition, one older patient and 12 parents underwent OGTTs. The mean blood glucose and insulin responses in young LS patients are illustrated in Fig 6. It is evident that at any age the LS patient had a slightly higher and delayed mean blood glucose response than the normal mean,[29] but this difference reached significance only in children and adolescents. In some pubertal or young adult patients, definite glucose intolerance was registered. Of interest is the fact that despite higher basal levels of insulin in childhood and puberty in LS patients, their mean peak insulin response during OGTTs was lower than the mean norm.[28] In addition, the insulin response was delayed as compared with the healthy population, but the differences did not reach significance because of the great individual variability. In LS patients older than 23 (n = 12), the low insulin response to an oral glucose load was even more evident (peak insulin, <100 μU/mL). Insulin determinations during OGTTs performed in two LS children younger than age 5 were noninformative. The decrease of the insulin response to the oral glucose load in young adults (23 to 33 years) with LS as compared with the pubertal group (11 to 22 years) was also evident when comparing the insulin area under the curve (0 to 180 minutes, 86.6 ± 47 *v* 184 ± 132, $P < .004$).

Of 12 parents who underwent an OGTT, four had glucose intolerance,[23] one of whom was homozygous for the disease subsequently developed overt diabetes, necessitating insulin treatment (Laron Z, Klinger, unpublished results).

EFFECT OF IGF-I TREATMENT

Intravenous or subcutaneous bolus injections of biosynthetic IGF-I (FK 780; Fujisawa, Osaka, Japan) to LS patients or healthy controls induced hypoglycemia but also a sharp suppression of insulin secretion and of GHRH, GH, and thyrotropin.[30,31] In subsequent long-term IGF-I treatment of children and adults with LS, it was found that in

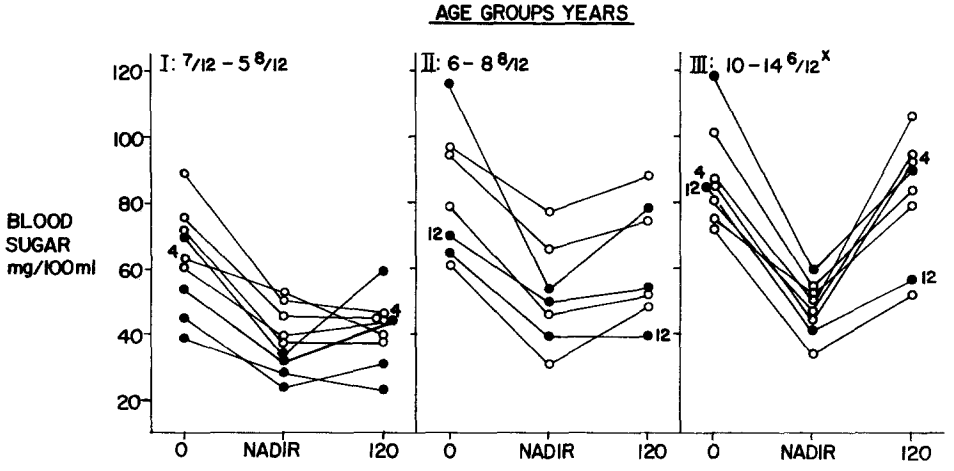

Fig 4. Glycemic response to an intravenous insulin bolus injection (0.5 U/kg) in children with LS. (○) Females; (●) males; X, including affected father aged 35 years. (Reprinted with permission.[23])

Table 2. Fasting Plasma Insulin in 30 LS Patients

Age (yr)	No. of Samples	Plasma Insulin (μU/mL) Mean ± SD	Range
0-5	21	10.1 ± 10.0	0.6-39
6-10	19	17.5 ± 11.4	4.0-40.2
11-22			
Total*	62	17.5 ± 12.0	2.0-72.1
Males†	25	13.8 ± 7.6	2.6-37.0
Females†	37	19.9 ± 13.8	2.0-72.1
23-38	33	7.6 ± 6.0	0.1-21.1

*Puberty in LS patients is delayed.[25]
†Males *v* females, $P < .03$.

addition to many metabolic effects and growth stimulation,[32-34] daily IGF-I administration (120 to 200 μg/kg) also causes reduction of the adipose tissue mass, as evidenced by skinfold measurements[32-34] (Fig 7). IGF-I also causes a persistent decrease of serum insulin levels,[34,35] leading to fewer hypoglycemic episodes and even a slight increase in GHb values (Laron Z, Klinger B, Avitzur Y, unpublished results, August 1995).

IGF-I treatment also persistently affected the glucose and insulin response during OGTT. In three of five adult LS patients, long-term IGF-I treatment decreased the insulin response and improved the glucose response (improved utilization?).[36] The effect of IGF-I treatment in one 13-year-old female LS patient is shown in Fig 8.

DISCUSSION

Long-term follow-up evaluation of a large cohort of untreated patients with GH resistance (Laron syndrome), ie, IGF-I deficiency, as well as subsequent treatment with exogenous IGF-I, enabled us to learn about differential metabolic effects of GH and IGF-I. One of the major conclusions was that most of the so-called metabolic and growth-promoting effects ascribed to GH are IGF-I–mediated. Of great interest were the dynamic changes in carbohydrate metabolism observed with advancing age in

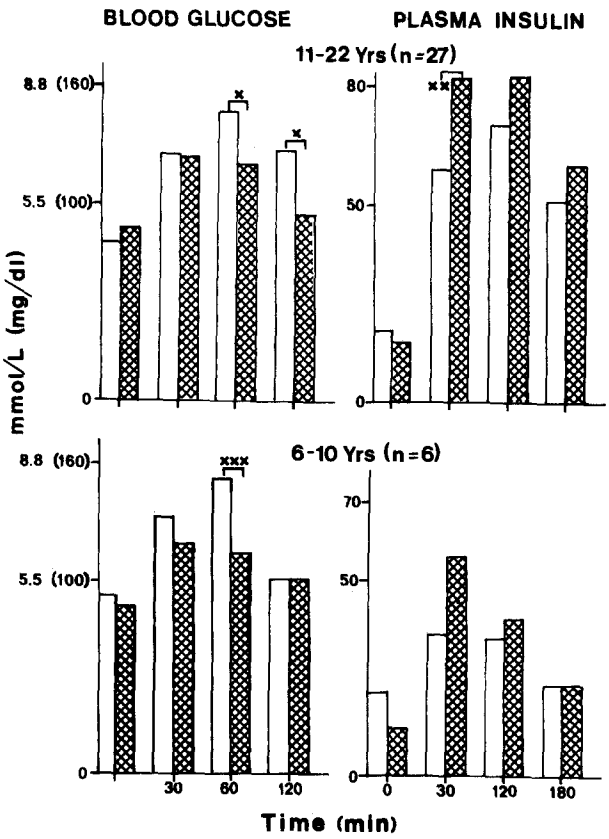

Fig 6. Mean blood glucose and insulin responses during OGTTs in young patients with LS (□). (▨) Normal. *$P < .0005$; **$P < .002$; ***$P < .005$.

untreated LS patients. Whereas in early childhood these patients had severe hypoglycemia, probably due to a low glucose output from the liver in the absence of IGF-I, they progressively developed relative hyperinsulinemia followed by hypoinsulinemia, glucose intolerance, and even diabetes from the onset of puberty onward. These changes occurred

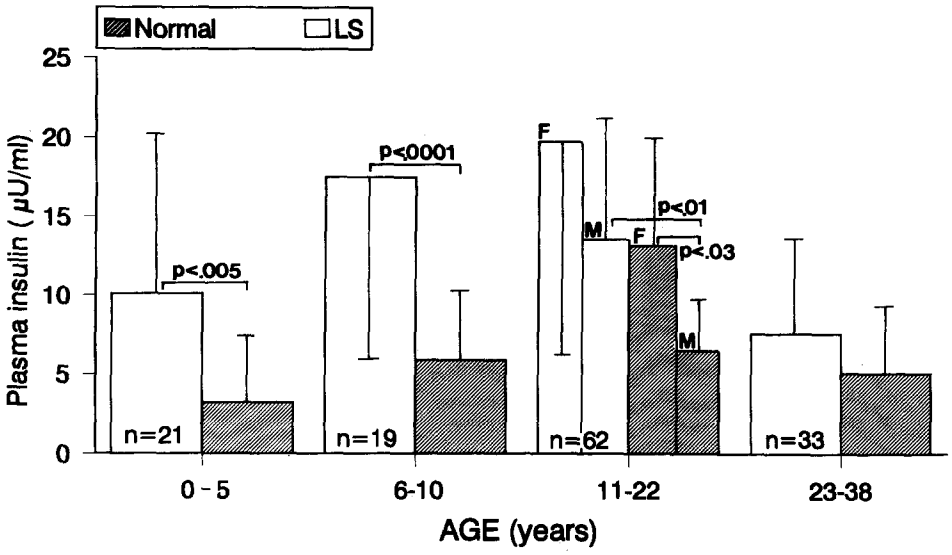

Fig 5. Overnight fasting plasma insulin levels (mean ± SD) in LS patients related to age groups. Normal ranges from Laron et al.[28]

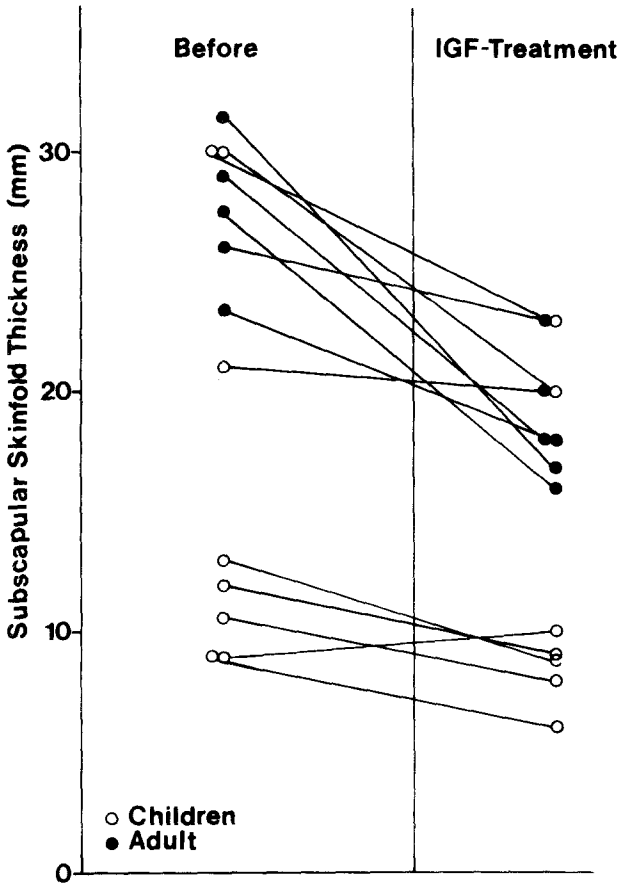

Fig 7. Reduction in adipose tissue mass (as measured by skinfold thickness) in LS patients treated with IGF-I.

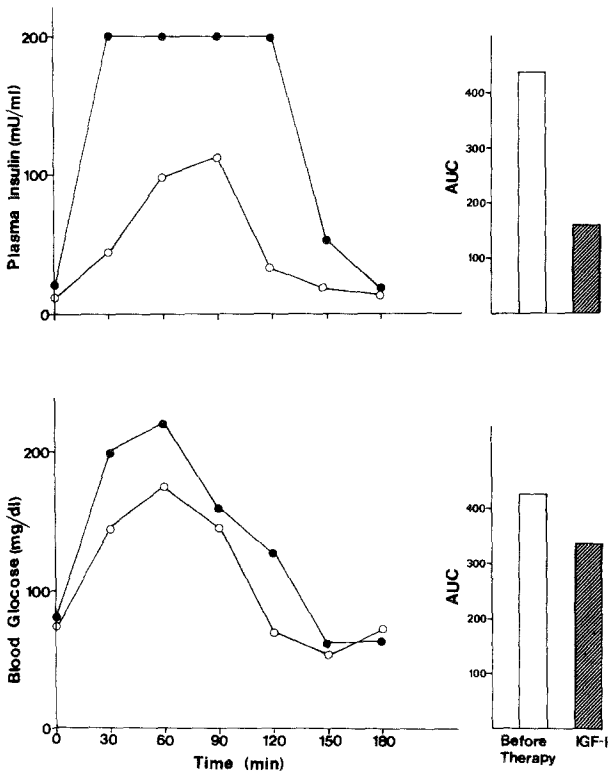

Fig 8. Glucose and insulin response during OGTT in a 13-year-old patient with LS before (●) and during IGF-I treatment (○).

concomitantly with progressive and excessive obesity. There were also elevated levels of total and low-density lipoprotein cholesterol[34,35] even in young adults. Comparing the insulin to glucose ratio, LS patients have excessive plasma insulin levels from childhood onward, ie, a state of beginning insulin resistance. With increasing adiposity and the onset of puberty, some patients developed glucose intolerance and hyperinsulinemia. In adulthood, a state of β-cell exhaustion developed, which led with advancing age to overt diabetes. It is not yet clear how IGF-I acts to induce the progressive insulin resistance, but it is possible that the latter is secondary to the marked obesity produced by lack of IGF-I. The finding that IGF-I treatment of LS patients improves both hypoglycemia of early age and also glucose intolerance and hypercholesteremia in pubertal or adult patients is of interest.[34,35]

In both instances, insulin secretion is decreased[30-35] when somatostatin secretion is stimulated (Laron Z, Gil-Ad, Koch Y, unpublished results, August 1995). The beneficial effect of IGF-I treatment in insulin-resistant diabetic patients has recently been described.[37,38]

The evidence that long-standing IGF-I deficiency, whether primary as in LS or secondary as in GH deficiency,[39] leads to obesity, glucose intolerance, and relative hyperinsulinemia makes one speculate as to whether the progressively decreasing secretion of GHRH-hGH and IGF-I with advancing adult age[40] may play a role in the development of non–insulin-dependent diabetes mellitus. If so, maybe administration of small doses of IGF-I to adults in whom a decrease in the activity of the GH axis is diagnosed[41] would be beneficial in decreasing the incidence of obesity and non–insulin-dependent diabetes mellitus.

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REFERENCES

1. Laron Z, Blum W, Chatelain P, et al: Classification of growth hormone insensitivity syndrome. J Pediatr 122:241, 1993

2. Eshet R, Laron Z, Pertzelan A, et al: Defect of human growth hormone receptors in the liver of two patients with Laron type syndrome. Isr J Med Sci 20:8-11, 1984

3. Godowski PJ, Leung DW, Meacham LR, et al: Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. Proc Natl Acad Sci USA 86:8083-8087, 1989

4. Meacham LR, Brown MR, Murphy TL, et al: Characteriza-

tion of a noncontiguous gene deletion of the growth hormone receptor in Laron's syndrome. J Clin Endocrinol Metab 77:1379-1383, 1993

5. Brown MR, Meacham LR, Pfaffle RW, et al: The molecular defect in Laron syndrome: Exon deletions. Pediatr Adolesc Endocrinol 24:127-131, 1993

6. Amselem S, Duquesnoy P, Duriez B, et al: Spectrum of growth hormone receptor mutations and associated haplotypes in Laron syndrome. Hum Mol Genet 4:355-359, 1993

7. Berg MA, Peoples R, Perez-Jurado L, et al: Receptor mutations and haplotypes in growth hormone receptor deficiency: A global survey and identification of the Ecuadorean E180 splice mutation in an oriental Jewish patient. Acta Paediatr 83:112-116, 1994 (suppl 399)

8. Laron Z, Klinger B, Erster B, et al: Serum GH binding protein activities identifies the heterozygous carriers for Laron type dwarfism. Acta Endocrinol (Copenh) 121:603-608, 1989

9. Leung DW, Spencer SA, Cachianes G, et al: Growth hormone receptor and serum binding protein: Purification, cloning and expression. Nature 330:537-543, 1987

10. Laron Z, Klinger B, Eshet R, et al: Laron syndrome due to a post-receptor defect: Response to IGF-I treatment. Isr J Med Sci 29:757-763, 1993

11. Laron Z, Pertzelan A, Karp M, et al: Administration of growth hormone to patients with familial dwarfism with high plasma immunoreactive growth hormone. Measurement of sulfation factor, metabolic and linear growth responses. J Clin Endocrinol Metab 33:332-342, 1971

12. Keret R, Pertzelan A, Zeharia A, et al: Growth hormone (hGH) secretion and turnover in three patients with Laron-type dwarfism. Isr J Med Sci 24:75-79, 1988

13. Laron Z, Pertzelan A, Mannheimer S: Genetic pituitary dwarfism with high serum concentration of growth hormone. A new inborn error of metabolism? Isr J Med Sci 2:152-155, 1966

14. Laron Z, Pertzelan A, Karp M: Pituitary dwarfism with high serum levels of growth hormone. Isr J Med Sci 4:883-884, 1968

15. Laron Z: Laron type dwarfism (hereditary somatomedin deficiency): A review, in Frick P, Von Harnack GA, Kochsiek K, et al (eds): Advances in Internal Medicine and Pediatrics. Berlin-Heidelberg, Germany, Springer-Verlag, 1984, pp 117-150

16. Rosenfeld RG, Rosenbloom AL, Guevara-Aguirre J: Growth hormone (GH) insensitivity due to primary GH receptor deficiency. Endocr Rev 15:369-390, 1994

17. Laron Z: Laron syndrome—From description to therapy. Endocrinologist 3:21-28, 1993

18. Rosenbloom AL, Guevara-Aguirre J: Bienvenidos a mi tierra de coledad: From poetry to molecular biology in Southern Ecuador. J Clin Endocrinol Metab 79:695-702, 1994

19. Laron Z, Parks JS: Lessons from Laron syndrome (LS) 1966-1992: A model of GH and IGF-I action and interaction. Pediatr Adolesc Endocrinol 24:1-367, 1993

20. Laron Z, Lilos P, Klinger B: Growth curves for Laron syndrome. Arch Dis Child 68:768-770, 1993

21. Laron Z, Pertzelan A, Karp M, et al: Laron syndrome—A unique model of IGF-I deficiency. Pediatr Adolesc Endocrinol 24:3-23, 1993

22. Laron Z: Prismatic cases: Laron syndrome (primary growth hormone resistance). From patient—to laboratory—to patient. J Clin Endocrinol Metab 80:1526-1531, 1995

23. Laron Z, Karp M: Carbohydrate metabolism in the syndrome of familial dwarfism and high plasma immunoreactive growth hormone (Laron type dwarfism), in Podolsky S, Viswanathan M (eds): Secondary Diabetes: The Spectrum of the Diabetic Syndrome. New York, NY, Raven, 1980, pp 363-371

24. Laron Z, Klinger B, Grunebaum M: Laron type dwarfism. Special Feature—Picture of the Month. Am J Dis Child 145:473-474, 1991

25. Laron Z, Klinger B: Body fat in Laron syndrome patients: Effect of insulin-like growth factor-I treatment. Horm Res 40:16-22, 1993

26. Laron Z, Sarel R, Pertzelan A: Puberty in Laron-type dwarfism. Eur J Pediatr 134:79-83, 1980

27. Pertzelan A, Lazar L, Klinger B, et al: Puberty in 15 patients with Laron syndrome: A longitudinal study. Pediatr Adolesc Endocrinol 24:27-33, 1993

28. Laron Z, Aurbach-Klipper Y, Flasterstein B, et al: Changes in endogenous insulin secretion during childhood as expressed by plasma and urinary C-peptide. Clin Endocrinol (Oxf) 29:625-632, 1988

29. Josefsberg Z, Vilunski E, Hanukuglu A, et al: Glucose and insulin responses to an oral glucose load in normal children and adolescents in Israel. Isr J Med Sci 12:189-194, 1976

30. Laron Z, Klinger B, Erster B, et al: Effects of insulin like growth factor in patients with Laron type dwarfism. Lancet 2:1170-1172, 1988

31. Laron Z, Klinger B, Silbergeld A, et al: Intravenous administration of rIGF-I lowers serum GHRH and TSH. Acta Endocrinol (Copenh) 123:378-382, 1990

32. Laron Z, Anin S, Klipper-Aurbach Y, et al: Effects of insulin-like growth factor on linear growth, head circumference and body fat in patients with Laron type dwarfism. Lancet 339:1258-1261, 1992

33. Laron Z: One year treatment with IGF-I of children with Laron syndrome. Clin Courier 11:7-8, 1993

34. Laron Z, Klinger B: IGF-I treatment of adult patients with Laron syndrome: Preliminary results. Clin Endocrinol (Oxf) 41:631-638, 1994

35. Laron Z, Klinger B, Jensen LT, et al: Biochemical and hormonal changes induced by one week of administration of rIGF-I to patients with Laron type dwarfism. Clin Endocrinol (Oxf) 35:145-150, 1991

36. Klinger B, Avitzur Y, Laron Z: Changing pattern with age of glucose tolerance in patients with Laron syndrome. Horm Res 41:85, 1994 (abstr 113)

37. Zenobi PD, Jaeggi-Groisman SE, Riesen WF, et al: Insulin-like growth factor-I improves glucose and lipid metabolism in type 2 diabetes mellitus. J Clin Invest 90:2234-2241, 1992

38. Schalch DS, Turman NJ, Marcsisin VS, et al: Short-term effects of recombinant human insulin-like growth factor I on metabolic control of patients with type II diabetes mellitus. J Clin Endocrinol Metab 77:1563-1568, 1993

39. Merimee TJ: The effect of growth hormone and insulin-like growth factor deficiencies on carbohydrate metabolism. Pediatr Adolesc Endocrinol 24:322-337, 1993

40. Ho KY, Hoffman DM: Physiology of growth hormone (GH) secretion: Implications for the diagnosis of GH deficiency in adults, in Laron Z, Butenandt O (eds): Growth Hormone Replacement Therapy in Adults: Pros and Cons. London, UK, Freund, 1993, pp 5-16

41. Gil-Ad I, Gurewitz R, Marcovici O, et al: Effect of aging on human plasma growth hormone response to clonidine. Mech Ageing Dev 27:97-100, 1984