Insulin-Like Growth Factor-I Decreases Serum Lipoprotein(a) During Long-Term Treatment of Patients With Laron Syndrome

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An increased circulating level of lipoprotein(a) [Lp(a)] is a well-recognized risk factor for coronary artery disease. While much remains to be understood about its regulation and physiological functions, we explored the effect of recombinant insulin-like growth factor-I (IGF-I) administration on circulating Lp(a) levels in 10 Laron syndrome (LS) patients (five children and five adults) with inherited IGF-I deficiency. There was no relationship between pretreatment or posttreatment Lp(a) levels and age and sex of the patients. With IGF-I treatment for 6 to 12 months, there was a significant reduction in Lp(a) (65.7% ± 15.5%, $P < .0001$) from the pretreatment level of 76 ± 45 mg/L to the posttreatment level of 29 ± 26 mg/L. This decrease was dosage-dependent on the IGF-I administered ($r = .685$, $F = 0.708$, $P = .029$) and correlated more strongly with the dosage ratio of the end to the beginning of treatment ($r = .78$, $F = 12.23$, $P = .008$). The higher the IGF-I dose and the higher the dose ratio, the greater the Lp(a) decrease and the lower the Lp(a) at the end of treatment. In conclusion, we observed a dose-dependent relationship between IGF-I administration and Lp(a) reduction in patients with LS. Further studies are needed to elucidate the mechanism of the effect, but our findings suggest a possible metabolic link between these two and shed more light on the regulation of apolipoprotein(a) [apo(a)] expression. It could also open an avenue for additional therapeutic usage of IGF-I.

LIPOPROTEIN (a) [Lp(a)] is an atherogenic low-density lipoprotein (LDL)-like cholesterol ester–rich plasma lipoprotein particle.[1-3] An elevated blood level of Lp(a) is a major risk factor for atherosclerosis. The gene for apolipoprotein(a) [apo(a)], the component of Lp(a) that distinguishes it from LDL, closely resembles the plasminogen gene. Thus, it has been postulated that the atherogenicity of Lp(a) could be mediated via both the LDL-like mechanism, ie, abnormal accumulation in the extracellular matrix of the arterial wall, and the plasminogen-like character, ie, inhibition of fibrinolysis by competition with plasminogen binding to fibrin.

Circulating levels of Lp(a) are strongly genetically regulated.[1-3] Interindividual differences in Lp(a) levels are large (>1,000-fold), and up to 90% of the interindividual variance could be explained by the apo(a) gene. It has been estimated that variable numbers of Kringle IV–like repeats manifested as apo(a) size-isoforms could contribute 40% to 60% of the genetic variance.[4] Other DNA variants of the apo(a) gene, including 5′ flanking, are thought to account for the rest.[5-7] The strong genetic regulation of circulating Lp(a) has been further supported by the findings that Lp(a) levels of children resemble closely those of their parents and are strongly associated with parental and grandparental histories of premature coronary artery disease.[8,9] From the first postnatal week in such children, Lp(a) begins to increase, reaching adult levels within the first year of life.[8] We have found no difference in Lp(a) levels among different age groups from 1-year-old babies to 65-year-old adults.[8,9]

Both experimental and epidemiological findings are consistent with the atherogenicity of elevated Lp(a), but the physiological functions of Lp(a) are still to be resolved. Although variations in Lp(a) levels within individuals are reportedly minimal, considerable intraindividual changes have been observed under various pathological conditions, particularly in end-stage renal disease.[10,11]

Although no pharmaceutical agents have been shown to decrease Lp(a) levels effectively and safely, except nicotinic acid to some extent,[12] there are data to suggest that several hormones, including insulin, estrogen, and triiodothyronine, may affect circulating Lp(a).[13-16] To explore further the hormonal influences on circulating Lp(a), we studied the effect of insulin-like growth factor-I (IGF-I) on circulating Lp(a) levels, since it is known that IGF-I replacement therapy in patients with Laron syndrome (LS) reduces both serum total and LDL cholesterol.[17-18]

SUBJECTS AND METHODS

Patients

Ten patients (five children and five adults) with LS[19-21] were studied. They are Jews of oriental origin. Pertinent clinical data are shown in Table 1.

All patients were part of a clinical trial with recombinant IGF-I (FK780; Fijusawa Pharmaceutical, Osaka, Japan). The drug was synthesized by recombinant DNA methods and has an amino acid sequence identical to that of natural IGF-I. The purity of the preparation (Lot no. 115707K, 115807K, and 710725K) is 97.2% as determined by reverse-phase high-performance liquid chromatography.

Freshly dissolved IGF-I was injected subcutaneously every morning before breakfast. The starting doses were 120 μg/kg body weight for adults and 200 μg/kg body weight for children. Doses were either unchanged or decreased during the course of treatment according to serum IGF-I levels. IGF-I doses at the end of the treatment period (12 months for children and 9 months for adults) are shown in Table 1. All patients were examined and measured at regular intervals, and blood samples were drawn for serum IGF-I and blood chemistry analysis after an overnight fast before treatment and again in the fasting state during treatment 24 hours after an IGF-I injection.

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Table 1. Pertinent Clinical Data of 10 Patients With LS at Initiation of IGF-I Treatment

Patient No.	Sex	CA (yr)	BA (yr)	Height cm	Height SDS	Weight (kg)	BMI (kg/m²)
1	M	0.5	Newborn	55.7	−5.0	5.1	16.4
2	M	3.3	1.5	69.0	−6.6	6.8	14.3
3	M	5.1	1.8	70.3	−8.0	6.7	13.7
4	F	11.6	11.0	118.8	−3.6	34.6	24.4
5	M	14.6	9.0	110.3	−6.5	25.5	21.1
6	M	28.1	Adult	138.6	−5.4	58.7	30.8
7	F	30.0	Adult	137.0	−5.5	54.6	29.1
8	F	30.3	Adult	118.0	−7.4	33.4	24.0
9	F	35.9	Adult	112.3	−8.0	39.0	31.1
10	F	39.7	Adult	121.3	−7.0	44.0	30.1

Abbreviations: CA, chronological age; BA, bone age; SDS, standard deviation score.

Lp(a) Quantitation

Serum samples were lyophilized before being shipped to the laboratory in Sydney. The lyophilized sera were then stored at −20°C, and were reconstituted in phosphate-buffered saline 2 hours before the assay. Lp(a) levels were measured by an enzyme-linked immunosorbent assay developed in our laboratory, with precision profiles described elsewhere.[22]

Statistical Analysis

We used a paired Student's *t* test to compare differences between pre- and post–IGF-I Lp(a) levels. Because of the skewed distribution of Lp(a), we also used Wilcoxon matched-pair rank comparison to assess significance. Relationships between Lp(a) levels and other quantitative variables including body weight, age, serum IGF-I levels, and body mass index (BMI) were evaluated with a stepwise linear regression model. Two-tailed *P* values are reported.

RESULTS

Serum IGF-I and Lp(a) Levels

Before IGF-I administration, the mean serum IGF-I levels were low (mean ± SD): 4.3 ± 1.1 nmol/L in children and 3.4 ± 8 nmol/L in adults. After 1 year of treatment in the children and 6 to 9 months in the adults, serum levels were increased to 10.1 ± 1.8 nmol/L ($P < .05$) and 16.1 ± 7.7 nmol/L ($P < .05$), respectively. The increase in serum IGF-I levels corresponded closely to a decrease in Lp(a) levels ($P < .01$). There was no correlation between fasting IGF-I levels and Lp(a) levels either at baseline ($r = .28$, $P = .43$) or 9 to 12 months after IGF-I replacement therapy ($r = .22, P = .45$).

Relationship Between IGF-I Treatment and Circulating Lp(a) Levels

Pretreatment Lp(a) levels of the five children (73 ± 21 mg/L; log 10, 1.81 ± 0.11 mg/L) and five adults (79 ± 22 mg/L; log 10, 1.83 ± 0.13 mg/L) were not different. There was no association between baseline Lp(a) level and age as reported in other studies.[8,9] We therefore compared the differences in serum Lp(a) levels resulting from IGF-I treatment by considering children and adults as one group. Lp(a) levels decreased markedly in every patient (Table 2). The posttreatment Lp(a) level (mean ± SD) was 29 ± 26 mg/L, and the mean log 10 level was 1.31 ± 0.39 mg/L. This was 65.7% ± 15.5% lower than the pretreatment level (76 ± 45 mg/L, and 1.82 ± 0.25 mg/L for log 10). The difference in absolute levels was 47 ± 28 mg/L (95% confidence interval, 27 to 67 mg/L). The difference was statistically significant by both paired Student's *t* test ($P = .0001$) and the Wilcoxon matched-pair rank test ($P = .0020$).

Baseline and posttreatment Lp(a) levels were not associated with age, BMI, sex, and serum IGF-I levels ($F = 1.66$, $P = .27$), but the percentage difference in Lp(a) levels was significantly related to the IGF-I dose at the end of 9 to 12 months of treatment ($r = .68$, $F = 7.08$, $P = .029$). When the ratios of IGF-I doses at the end to the beginning of treatment were entered into the stepwise regression model, the dose ratio was highly associated with the percentage decrease in Lp(a) levels ($r = .78$, $F = 12.23$, $P = .0081$) with a regression coefficient of 49.5% (95% confidence interval, 16.8% to 82.1%). This dose ratio was also negatively associated with the log Lp(a) levels at the end of treatment ($r = -.80$, $F = 13.9$, $P = .0059$), a relationship much stronger than that between the absolute IGF-I dosage administered and the Lp(a) level at the end of treatment ($r = -.571, F = 0.388, P = .084$). Thus, the higher the IGF-I dosage used at the end of treatment, the greater the reduction in Lp(a) levels. The end- to beginning-dose ratio of IGF-I treatment was the strongest positive predictor for the extent of Lp(a) reduction during treatment.

DISCUSSION

LS, first described in 1966,[19] presents a unique model to study the effects of IGF-I deficiency starting in utero.[23] It is clinically characterized by dwarfism, acromicria, small head circumference, and progressive obesity.[24,25] The laboratory findings are high serum growth hormone (GH) levels with

Table 2. Lp(a) Levels in Patients With LS Before and During IGF-I Treatment

Patient No.	Sex	CA (yr)	IGF-I Treatment Pre	IGF-I Treatment Post	Difference (mg/L)†	Duration of Treatment (mo)
1	M	0.5	72	15	57 (79.2%)	12
2	M	3.3	152	36	116 (76.3%)	12
3	M	5.1	59	25	34 (57.6%)	12
4	F	11.6	40	10	30 (75.0%)	12
5	M	14.6	41	11	30 (73.2%0	12
6	M	28.1	70	37	33 (47.1%0	9
7	F	30.0	153	92	61 (39.9%)	9
8	F	30.3	103	50	53 (51.5%)	9
9	F	35.9	35	5	30 (85.7%)	6
10	F	39.7	35	10	25 (71.4%)	6
Total (mean ± SD)			76 ± 45	29 ± 26	47 ± 28* (65.7% ± 15.5%)	

*$P < .0001$ by paired Student's *t* test.

†Pretreatment minus posttreatment (percentage decrease in parentheses).

low to undetectable circulating IGF-I.[26] The disease is due to either molecular defects of the GH receptor or a postreceptor defect.[27-30] The deficiency of IGF-I leads to a series of biochemical and metabolic changes that include hypoglycemia, hypophosphatemia, low liver enzymes, and low glomerular filtration rate.[20,24,31] Other biochemical abnormalities observed include a progressive increase in blood cholesterol, mainly the LDL fraction,[32] glucose intolerance, and insulin resistance.[33] IGF-I treatment decreases subcutaneous fat tissue and reduces both total and LDL cholesterol levels, mainly in adult patients who were more obese and had abnormally high lipid levels.[18,32]

The present investigation shows for the first time that basal serum Lp(a) levels in patients with this syndrome are significantly reduced by IGF-I administration in a dose-dependent manner. This decrease was observed in adults and children, and was independent of sex, age, BMI, body weight, and the period of IGF-I treatment. Neither pretreatment nor posttreatment Lp(a) levels were associated with corresponding serum IGF-I levels, but the changes in IGF-I levels over the treatment period were negatively correlated with the changes in Lp(a) levels. Furthermore, when changes in the doses of recombinant IGF-I administered (expressed by the ratio of the two) were entered into the model, the dosage change was the only predictor for the Lp(a) reduction. Posttreatment Lp(a) levels were also determined by the dose ratio. These findings may indicate a gradual effect on Lp(a) levels induced by the gradual change in IGF-I dose during the treatment period. In support of this, IGF-I levels measured and the dosage of IGF-I administered at a single point of time showed much less correlation with the changes in Lp(a) levels. Instead, the change in IGF-I dosage was most strongly associated with the change in Lp(a) level. However, since baseline Lp(a) levels in all our patients were less than 200 mg/L, it would be of interest to see whether this lowering effect is also observed in patients with Lp(a) levels above 300 mg/L—the level reported to be associated with increased coronary artery disease risk.[1-3] Although lyophilization may artifically decrease the original Lp(a) level,[34,35] the observed changes in Lp(a) over the treatment period are unlikely to be affected, since the effect of lyophilization would be equal on both serum samples collected from the same patient.[35]

The mechanism of the IGF-I–induced effect on circulating Lp(a) levels remains speculative, but the magnitude of the dose-dependent decrease was sufficiently large to suggest a direct effect of IGF-I on apo(a) expression. Apo(a) is the unique carrier protein of Lp(a) and determines the circulating levels. However, an indirect effect via some other concomitant metabolic change may be relevant. Administration of insulin has been shown to increase Lp(a) levels.[13] IGF-I, as a constitutively expressed growth factor, has diverse metabolic effects essential for normal growth. Thus, determining whether the endogenous IGF-I could have a similar effect on Lp(a) levels in vivo would also be of great interest and important for understanding the physiological regulation of Lp(a) expression.

Another important issue is whether individuals with inherited IGF-I deficiencies such as LS have higher Lp(a) levels than the healthy population. Due to the remarkably large interindividual variation in Lp(a) levels,[1-3] it is not valid to compare baseline Lp(a) levels of these 10 LS patients with those of healthy controls. A much larger patient population would be needed. Nevertheless, Lp(a) levels among these 10 LS patients are within the range observed in healthy white populations.[36]

In conclusion, our study shows for the first time that IGF-I administration results in a highly significant dose-dependent reduction in Lp(a) levels in patients with LS. Although further studies are needed to elucidate the mechanism of the effect, it is nevertheless suggestive of a possible metabolic link between IGF-I and Lp(a) that may be relevant to an understanding of the regulation of apo(a) expression. It could also open an avenue for additional therapeutic usage of IGF-I.

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