CLINICAL STUDY

Total and high molecular weight adiponectin are elevated in patients with Laron syndrome despite marked obesity

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Abstract

Objective: Patients with Laron syndrome (LS; primary GH insensitivity) caused by molecular defects of the GH receptor gene, are characterized by dwarfism, profound obesity, and hyperlipidemia. The aim of the current study was to evaluate adiponectin levels in LS, as obesity is known to be associated with low adiponectin.

Design and methods: We studied nine untreated LS adult patients (5 males, 4 females) and six girls with LS receiving once-daily treatment by IGF1. Total and high molecular weight (HMW) adiponectin levels, adiponectin multimers distribution, and metabolic indices were analyzed in serum samples obtained during several years of follow-up.

Results: Adiponectin levels in the severely obese adult LS patients (percent body fat; females $61.0 \pm 2.5\%$, males $40.6 \pm 8.1\%$) were two- to three-fold higher than those reported for subjects of corresponding age, gender and degree of adiposity. Total adiponectin was significantly higher in females compared with males (21.4 ± 3.5 vs 10.2 ± 4.6 $\mu\text{g/ml}$, $P < 0.001$). The elevated adiponectin in LS subjects was associated with an increased abundance of the HMW isoform, and positively correlated with body fat percentage ($r = 0.65$, $P = 0.017$) and leptin ($r = 0.65$, $P = 0.012$). There was no correlation between adiponectin levels (total and HMW) and the degree of insulin resistance in LS subjects or their blood lipids levels. Adiponectin was also high in young girls with LS (22.9 ± 7.4 $\mu\text{g/ml}$) and did not change during long-term IGF1 replacement therapy.

Conclusion: Adiponectin hypersecretion in LS, despite profound obesity, suggests that GH activity may negatively impact adiponectin secretion from adipocytes.

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Introduction

Laron syndrome (LS; primary GH insensitivity or resistance, OMIM #262500) is a rare autosomal recessively inherited disease found mainly in consanguineous families originating from Mediterranean, Mideastern or south Asian regions or in their descendants (1–5). It is caused by deletions (6) or mutations in the GH receptor gene (2–4, 7, 8), resulting in the absence of GH activity, and congenital insulin-like growth factor-1 (IGF1) deficiency (2). The only treatment is IGF1 replacement therapy (9).

One of the phenotypical characteristics of LS, in addition to dwarfism, is profound obesity (10–12), noticed already in early infancy (13), which does not decrease during long-term IGF1 treatment (14). Concomitantly with a marked increase in subcutaneous and

visceral fat (2, 12), the majority of patients with LS progressively develop signs of the metabolic syndrome like hyperlipidemia (11) and nonalcoholic fatty liver disease (15).

Adiponectin is the most abundant hormone produced by the adipose tissue of humans and rodents and has insulin-sensitizing and anti-atherogenic properties (reviewed in (16, 17)). It circulates in three distinct multimers: trimers, hexamers and larger multimers of 12–18 subunits (high molecular weight, HMW); the latter appears to be the most active form of the hormone (16, 17). Adiponectin levels differ with age, gender and obesity. At birth, adiponectin levels are extremely high (18–20) and fall off gradually until puberty (19, 21). During pubertal development an additional progressive decline in adiponectin levels occurs mainly in boys, which leads to lower adiponectin levels compared

with girls. This decline is strongly associated with androgen levels and accounts for the gender differences seen in adults (21).

Unlike most other adipocytokines that increase with the excess of body fat mass, adiponectin levels are markedly reduced in obesity, in both adults and children (21–25) and negatively correlate with body mass index (BMI) and percent body fat. The decrease in adiponectin in obesity is probably due to reduced concentrations of the HMW adiponectin isoform (26–28). It was therefore of interest to determine the serum levels of adiponectin and the HMW adiponectin multimer in both untreated adult patients with LS and in children with LS undergoing IGF1 treatment, all very obese. This paper presents the unexpected results of this investigation.

Subjects and methods

Subjects

All the patients with LS were followed and treated at the Endocrinology and Diabetes Research Unit, Schneider Children's Medical Center of Israel. Nine untreated adult LS patients aged 29–53 years, (5 males, 4 females) and 6 girls (5–16 years) receiving once daily treatment by IGF1 (120–180 µg/kg s.c.; Fujisawa, Osaka, Japan) were investigated. The diagnosis of LS in these patients was ascertained using the IGF1 generation test (2) and by molecular analysis of the GH receptor gene (5). The pertinent clinical data of the patients, arranged by gender and age, are shown in Tables 1 and 2. Of note, due to underdevelopment of the muscular and skeletal systems in the patients with LS (2), the BMI does not accurately reflect the degree of obesity in these subjects (12, 14). Therefore, percentage of body fat estimated by dual-energy by X-ray absorptiometry (DEXA) and not

BMI was used in this study as a measure of adiposity. In addition, no ideal control group to match the dwarfism and severe obesity of LS patients was available; hence, our data was compared to existing data in the literature for morbidly obese subjects of normal stature (Table 3). This comparison employed only data obtained with the same analytical methodology used in the current study to measure adiponectin and leptin concentrations. The study was approved by the Hospital Ethical Committee and the patients or their parents signed an informed consent form.

Methods

Hormonal assays Blood samples were collected from all participants during their long-term follow-up. Blood was drawn after an overnight (12–14 h) fast, serum samples were separated and analyzed for general blood chemistry and insulin at the same day. For adiponectin and leptin measurements, samples were stored at -30°C and analyzed together. Total adiponectin and leptin were determined by RIA (Linco, Millipore, St Charles, MO, USA; 18, 29) and the HMW-adiponectin was measured by HMW-adiponectin ELISA kit (Otsuka Pharmaceutical Co. Ltd, Tokyo, Japan) (30). The interassay coefficient of variations (CV) for leptin, adiponectin, and HMW-adiponectin were <6.2 , <9.3 , and $<10\%$ respectively. Intra-assay CV for each of the three were <8.3 , <6.5 , and $<10\%$ respectively. The distribution of adiponectin multimers in serum samples was analyzed under nonreducing and nondenaturing conditions as described previously (29, 31). Abundance of adiponectin multimers was determined by densitometry. Insulin was determined by a solid-phase two-site chemiluminescent immuno-metric assay (Immulin 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA) and

Table 1 Anthropometric and hormonal parameters of untreated adults and insulin-like growth factor-1 (IGF1) treated pediatric patients with Laron syndrome during long-term follow-up.

	Adults		Children
	Males $n=5$, $x=9$	Females $n=4$, $x=6$	Females $n=6$, $x=26$
Age (years)	39.4±8.2 (29–51)	48.8±5.1 (43–53)	10.4±3.7 (5–16.6)
Height (m)	1.3±0.1 (1.16–1.40)	1.25±0.1 (1.12–1.36)	1.15±0.15 (0.89–1.41)
Weight (kg)	46.4±13.4 (27.9–66)	47.5±9.3 (44–60)	33.8±18.1 (12.3–70.1)
Body fat (%) by DEXA	40.6±8.1 (31.6–49.7)	61.0±2.5* (58.5–64.5)	46.5±13.5† (25.0–62.8)
Adiponectin (µg/ml)	10.2±4.6 (6.5–21.1)	21.4±3.5* (15.9–25.1)	22.9±7.4 (15–32.5)
HMW adiponectin (µg/ml)	5.3±3.4 (1.7–12.5)	15.4±2.3* (13.0–17.6)	19.2±4.9 (13.7–26.8)
Leptin (ng/ml)	11.3±4.9 (6.1–19.7)	27.9±2.7* (25–31.8)	27.3±5.3 (9.2–63.4)
Leptin/adiponectin ratio $\times 10^{-3}$	1.2±0.7 (0.29–2.52)	1.4±0.2 (1.11–1.57)	1.2±0.7 (0.63–3.11)
Insulin (µIU/ml)	3.8±1.4 (2–5.2)	5.0±3.8 (2–10.1)	5.1±4.2 (2–11.9)
Glucose (mg/dl)	84.2±12.2 (74–99)	82.3±5.7 (74–87)	80.1±7.4 (69–87)
HOMA-IR	0.77±0.31 (0.49–1.23)	1.02±0.65 (0.42–2.16)	1.12±0.97 (0.34–2.82)
Total cholesterol (mg/dl)	146.8±28.9 (195–248)	232.3±25.2 (218–270)	170.5±22.8† (129–205)
Triglycerides (mg/dl)	115.8±49.6 (48–157)	135±13.9 (117–151)	77.4±25.5† (50–101)

Data are means $\pm$ s.d., ranges in parentheses. n , number of patients in the indicated group; x , number of samples in the indicated group, obtained from patients at different time points during their long-term follow-up. * $P<0.05$ females versus male LS patients. † $P<0.05$ girls versus female LS patients. Some of the LS adults with hyperlipidemia received statin therapy.

Table 2 Serum adiponectin and leptin in girls with Laron syndrome during long-term insulin-like growth factor-1 (IGF1) treatment^a.

Patient no.	Age (years)	Ht (m)	Wt (kg)	% Body fat	Adiponectin (μg/ml)	Leptin (ng/ml)
1	5	0.96	17	47	25.7	5.4
	5.3				28.1	13
	6	0.98	19		22.2	14
	6.2				25	18
	6.5				19.4	13.3
2	7	1.03	18.6	25	29.8	11.8
	6	0.89	12.3		24.8	16.8
	6.3				15	17.9
3	9	1.1	25.2	49.1	17.0	12.2
	9.6				23.8	20
	10	1.12	27.6		16.4	21.9
	10.4				18.5	33.1
	10.8				18.9	14.4
4	11	1.14	27.8		19.9	21.4
	9.5	1.16	30		20.3	17.5
	10	1.19	30		23.1	19.1
5	12	1.07	25	48.7	27.7	56.1
	12.3				25.9	42.1
	13.2	1.14	30		24.9	47.8
	13.6				20.8	49.8
	13.9				31.5	40.5
6	14.3	1.19	33	62.8	32.5	63.4
	15	1.38	64		15.2	47.2
	15.5	1.39	72		26.1	35.5
	16	1.41	70.1		19.4	33.9
	16.6	1.41	70.1		22.9	23.5

^aAll samples were obtained during IGF1 therapy (9), with one exception (first sample of patient 2).

blood chemistry by a Hitachi autoanalyzer. Insulin resistance was estimated by the homeostasis model assessment insulin resistance index (HOMA-IR; 32) and HOMA index was calculated according to the formula: glucose (mmol/l) × insulin (µU/ml)/22.5.

Body composition Body fat was determined using DEXA (Model DPX-IQ 8565-A, Lunar Radiation Corp., Madison, WI, USA).

Data analysis

Data are presented as means ± s.d. Statistical analyses were performed using Student's *t*-test for two-group

comparisons. Spearman's correlation analysis was used to examine bivariate relationships. Significance tests were two-tailed, and *P* values < 0.05 were considered as statistically significant. Calculations were performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA).

Results

Anthropometric and hormonal data of LS patients

Forty-one sera from 15 patients with LS (9 adults and 6 IGF1-treated children), obtained during long-term

Table 3 Comparison of mean serum adiponectin and leptin levels in Laron syndrome (LS) patients and subjects with a similar degree of obesity.

Group	Age	% Body fat (by DEXA)	Adiponectin (µg/ml)	Leptin (ng/ml)	Reference
LS females	48.8 ± 5.1	61.0 ± 2.5	21.4 ± 3.5	27.9 ± 2.7	This study
Obese females	42.0 ± 3.0	50.5 ± 3.6	5.0 ± 2.2	31.3 ± 12	(36)
Obese females	37.7 ± 9.6	47.8 ± 5.1	11.4 ± 4.3	NA	(37)
LS males	39.4 ± 8.2	40.6 ± 8.1	10.2 ± 4.6	11.3 ± 4.9	This study
Obese males	25.0 ± 4.1	41.1 ± 8.3	6.0 ± 4.1	NA	(38)
LS girls	10.4 ± 3.7	46.5 ± 13.5	22.9 ± 7.4	27.3 ± 5.3	This study
Obese girls	10.8 ± 3.8	41.4 ± 4.8	11.9 ± 5.2	30.2 ± 16.8	(42)
Obese girls	11.2 ± 3.6	41.2 ± 5.2	12.0 ± 5.1	26.8 ± 13.5	(40)
Obese girls	13.1 ± 1.8	41.4 ± 4.8	9.6 ± 3.0	NA	(41)
Obese girls	11.1 ± 0.2	40.6 ± 0.6	10.0 ± 0.4	31.1 ± 1.5	(43)

NA, not available.

This comparison employed only data obtained with the same analytical methodology used in the current study to measure adiponectin and leptin concentrations (RIA, Linco).

follow-up were analyzed. Anthropometric data of the patients as well as mean levels of total and HMW-adiponectin, leptin, circulating lipids, insulin, glucose, and HOMA-IR are shown in Table 1. As shown, all LS patients are very short and very obese (Table 1) with body fat above normal and higher than what we usually measure in obese subjects (33). Adult female subjects have significantly higher BF% than males ($P < 0.01$). Percent body fat of our adult LS female subjects was 59–65% compared to 36–51% in age matched healthy controls (33) and a body fat of 32–50% in the adult LS males compared to 12–37% in healthy male subjects of the same age range (33).

Adiponectin and leptin levels in adult untreated LS patients

Despite their profound obesity, the adult LS patients have both high total adiponectin and high leptin levels (Table 1, Fig. 1A and B), with both adipokines (Fig. 1A and B) being significantly higher in the female compared with the male LS patients (adiponectin; 21.4 ± 3.5 vs 10.2 ± 4.6 $\mu\text{g/ml}$, $P < 0.001$ and leptin; 27.9 ± 2.5 vs 11.3 ± 4.9 ng/ml , $P < 0.001$).

Unlike the well established negative correlation of total adiponectin with the degree of obesity and with leptin levels found in the general population (22, 24, 25), adiponectin levels in the adult LS subjects were positively correlated with the percent of body fat ($r = 0.65$, $P = 0.017$) and leptin levels ($r = 0.65$, $P = 0.012$). No correlation was observed between adiponectin levels and a variety of metabolic parameters, including blood lipids, HOMA-IR, and insulin levels.

To further examine adiponectin characteristics in LS patients, we compared the distribution of the distinct adiponectin multimers in the sera of LS females and healthy lean females (29; Fig. 2). While previous studies have demonstrated that the HMW adiponectin isoform is markedly reduced in obese subjects compared with lean counterparts (27, 28), in the severely obese LS females the abundance of the HMW isoform was

threefold higher ($P = 0.01$) than in the lean controls (Fig. 2A) and accordingly, the ratio of HMW/total adiponectin was significantly higher in the LS females ($P < 0.001$) than in the lean controls (Fig. 2B). No significant differences were found in the abundance of the hexamer ($P = 0.38$) and trimer ($P = 0.2$) isoforms in sera of LS and lean control women. In addition, circulating HMW-adiponectin and total adiponectin levels in adult LS patients (Table 1) were highly correlated with each other ($r = 0.92$, $P < 0.001$). Similar to our findings for total adiponectin, the HMW adiponectin levels were significantly higher in female compared with male LS patients (15.4 ± 2.3 vs 5.3 ± 3.4 $\mu\text{g/ml}$, $P < 0.001$) and positively correlated with the percent of body fat ($r = 0.64$, $P = 0.05$) and leptin levels ($r = 0.69$, $P = 0.03$), but not with any of the metabolic indices.

Adiponectin and leptin in IGF1 treated LS girls

We studied 6 girls with LS, aged 5–15 years, during 3–28 months of IGF1 therapy. The longitudinal changes in adiponectin and leptin levels during the follow-up period, along with changes in their height and weight, are illustrated in Table 2. With one exception (patient 2, Table 2) for whom we had a pretreatment blood sample, adiponectin and leptin levels measurements were performed in blood samples obtained during IGF1 therapy. Unlike obese girls of similar age and degree of adiposity (23), the pretreatment adiponectin levels in patient 2 were high (24.8 $\mu\text{g/ml}$) and decreased after 3 months of IGF1 therapy (15 $\mu\text{g/ml}$). Adiponectin levels in the other five IGF1 treated girls were also very high, despite being markedly obese (Tables 1 and 2, Fig. 1A). As shown in Table 2, despite fluctuations adiponectin levels did not change significantly during the longterm IGF1 therapy; however, we cannot exclude the possibility that at the beginning of therapy, the adiponectin levels were higher, as seen in patient 2. In accordance with their profound obesity, leptin concentrations in the LS girls were very high (Tables 1 and 2, Fig. 1B). It is noteworthy that leptin levels were higher in the older than the younger girls, most likely due to their higher degree of obesity, whereas adiponectin levels were not considerably different between the age groups. Adiponectin levels of adolescent girls with LS (patients 3–6, Table 2) were significantly elevated compared with levels we measured in another study (34) for lean ($P < 0.05$) and obese ($P < 0.001$) girls of similar age.

Similar to our observations in adults, there was a statistical positive correlation between adiponectin and leptin ($r = 0.55$, $P = 0.02$) in the adolescent girls with LS. We could not evaluate the association between adiponectin or leptin and the degree of obesity, due to the small number of body fat composition measurements in the LS girls.

Figure 1 Individual adiponectin levels (A) and leptin levels (B) in LS patients. M, male; F, female; mean value in each group is indicated by a line.

Figure 2 Distribution of adiponectin multimeric forms in serum of females with LS and healthy lean females. Adiponectin multimer distribution was analyzed in serum samples of four LS females (LS) and four healthy lean females (BMI, 20.2 ± 2.1 kg/m²; CON). 0.5 μ l of serum were subjected to 5–15% SDS-PAGE under nonreducing and nonheat-denaturing conditions. Adiponectin was detected by a specific antibody (Chemicon). (A) Three different molecular weight groups were detected in all samples: High molecular weight (HMW), hexamer (Hex), and trimer (Tri). The abundance of specific adiponectin multimers was quantified by densitometry of the relevant bands. (B) The relative proportion of each multimer to total adiponectin (% of total adiponectin) was obtained by dividing band density of the specific multimer by total density in each lane. * $P < 0.001$ HMW/Total adiponectin ratio – LS versus CON. # $P < 0.001$ Hex/Total adiponectin ratio – LS versus CON.

Discussion

LS is an interesting model for studying adiponectin physiology. The key observation in the current study was that patients with LS, who are GH insensitive and IGF1 deficient, have elevated adiponectin levels, despite being severely obese. The elevated adiponectin levels were accounted for largely by the HMW adiponectin isoform. Adiponectin concentrations of both female and male adult LS patients were considerably higher (two- to three-fold), compared to reported data for obese subjects of similar age, gender and with an equivalent degree of adiposity (Table 3), whereas leptin levels were comparable (24, 25, 35–38). In addition, when adiponectin levels in LS females were normalized for individual body fat percent, they were higher (0.36 ± 0.06), compared with reported data for obese healthy women (0.17 – 0.21 ; 35, 39). Similar to adults, adiponectin levels in the girls with LS were significantly higher compared with healthy girls of similar age and degree of adiposity

(Table 3; 40–43). Contrary to the healthy population, total and HMW adiponectin in LS patients positively correlated with the degree of adiposity and leptin levels.

Our findings of high adiponectin in patients with GH insensitivity are supported by similar observations in the GH receptor knockout mice (44, 45). Furthermore, GH suppressed adiponectin secretion in *in vitro* cultured human adipose tissue (45), and GH treatment of prepubertal short stature children resulted in decreased serum adiponectin levels (46). Collectively these findings raise the intriguing possibility that GH activity may negatively affect adiponectin production or secretion from adipocytes; however, the mechanism underlying this process is as yet unclear. It may be attributed to loss of a direct suppression of adiponectin synthesis or secretion by GH, as the GH receptor is expressed in adipocytes, or alternatively to repression by IGF1 or IGF binding protein-3 (IGFBP-3), known to be deficient in LS (2, 47). Indeed, suppressive effects of GH and IGFBP-3 on adipocyte secretion of adiponectin are supported by recent *in vitro* and *ex vivo* studies (45, 48). Unlike GH and IGFBP-3, *in vitro* studies did not support an inhibitory effect of IGF1 on adiponectin secretion (49). Our observation that the elevated adiponectin levels in LS children did not change significantly and consistently during prolonged IGF1 treatment may support this notion, but the lack of sufficient observations before initiation of IGF1 treatment prevents a definite conclusion. It is noteworthy that in addition to LS, high adiponectin levels were documented in patients with Prader–Willi syndrome (PWS), who have diminished GH secretion (50) as well as in fetuses at late gestation or newborns (20), who have significantly lower numbers of GH receptors compared with the postnatal state (51). These observations lend further support to the hypothesis that GH activity is an important modulator of adiponectin levels.

The biosynthesis of adiponectin multimers is a complex process involving extensive post-translational modifications, which are necessary for the intracellular assembly and stabilization of its HMW multimers (28). The secretion of these multimers from adipocytes is tightly controlled by a pair of molecular chaperones in the endoplasmic reticulum, ERp44 and Ero1- α , known to be regulated by the metabolic state of the cell and PPAR γ agonists, and to display sexual dimorphism (52). Our findings that GH insensitivity is associated with high circulating adiponectin levels, combined with a shift towards the HMW forms, raises an intriguing possibility that GH activity may affect adiponectin secretion by modulating the levels of these chaperons. Further research will be required to address this hypothesis.

GH plays a critical role in the regulation of body composition and both children and adults with GH deficiency or GH insensitivity present with increased adiposity and decreased lean body mass (2–4). Accumulating data obtained from magnetic resonance

imaging (MRI) measurements of abdominal subcutaneous and visceral fat depots in healthy obese adults and children support the notion that excessive visceral rather than subcutaneous adiposity is associated with decreased production and circulating levels of adiponectin (53, 54). Contrary to healthy obese subjects, MRI studies in patients with PWS, who have diminished GH secretion, revealed an unusual situation in which their increased obesity is associated with a relative reduction in visceral adiposity (55). Based on these findings it was proposed (50) that the elevated adiponectin in PWS subjects is a reflection of their proportionately lesser amount of visceral adiposity. As obesity in LS affects both the trunk and the limbs (2, 12, 14), with a great proportion of their fat being localized subcutaneously, in addition to around the visceral organs (2, 12), it is appealing to examine whether alterations in body fat depots distribution underlie the dissociation between hyperadiponectinemia and adiposity in LS patients. MRI studies, to determine the ratio of visceral to subcutaneous adiposity in adults and children with LS, will be necessary to test this hypothesis.

Interestingly, despite their profound obesity, HOMA-IR was abnormal (2.2) in only one adult LS patient, in marked contrast to morbidly obese subjects who display a high degree of insulin resistance with HOMA-IR values of 5–9 (56, 57). A similar dissociation between profound obesity and insulin resistance was observed in the GH receptor KO mice (44, 45). Using a mouse model with chronic GH deficiency it was recently demonstrated that GH insensitivity is associated with decreased p85 α expression and improved insulin receptor substrate (IRS)-1-associated PI3 kinase activity in the adipose tissue, leading to enhanced insulin sensitivity in conjunction with increased lipid deposition and enhanced adiponectin secretion (58). This provides an explanation for the insulin hypersensitivity and associated obesity and hyperadiponectinemia of the GH-insensitive mice (58), as well as for the lower than expected insulin resistance in LS patients in relation to their profound obesity.

One limitation of our study lies in the relatively small number of subjects in each LS group, as LS is a rare disease with a very small number of affected subjects worldwide; in addition, the lack of an obese control group limits the interpretation of the results of the present study.

In conclusion, adiponectin levels in patients with LS and GH insensitivity are elevated, despite their marked obesity. Our findings highlight the complex regulation of adiponectin secretion from adipocytes and underline the negative role of GH function on adiponectin secretion. In addition to the contribution of our novel findings in the understanding of adiponectin regulation, other clinical implications can be envisaged. As high adiponectin is associated with a lower risk for cancer development (59, 60), it is possible that the high adiponectin levels in LS patients contribute to the

mechanism which protects patients with LS from malignancies (61).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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