

Supplementary Table 1. Effect of metreleptin replacement therapy on glucose metabolism in the combined group of FPLD patients with severe and moderate hypoleptinemia.

Variable	All subjects (n=24)			P value
	0 mo	3 mo	6 mo	
Fasting plasma glucose (mg/dL)	111.4 ± 37.2 (24)	106.6 ± 377 (22)	101.6 ± 28.4 (20)	0.06
Fasting serum insulin* (μU/mL)	35.3 (20.7-91.9) (11)	24.5 (18.3-43.1) (12)	18.7 (17.8-28.8) (9)	0.04
Hemoglobin A1c (%)	6.5 ± 1.7 (24)	6.3 ± 1.8 (21)	6.5 ± 2.0 (19)	0.59
K <sub>ITT</sub> (%)	1.02 ± 0.54 (20)	1.26 ± 0.49 (14)	1.25 ± 0.53 (15)	0.007
Glucose <sub>AUC</sub> *	18839 ± 3385 (13)	17808 ± 3870 (13)	182221 ± 4018 (11)	0.28
Insulin <sub>AUC</sub> *	39521 (19172-70095) (11)	28011 (16366-45879) (12)	19133 (14889-50852) (9)	0.03

P values in the last column represent the linear trend over Month 0, Month 3, and Month 6 using mixed model repeated measures analysis. Bottom numbers in parentheses indicate total number of subjects for whom the data were available.

\* measured only in those not on insulin or oral hypoglycemic therapy. Results are presented as mean ± SD or median (25<sup>th</sup> to 75<sup>th</sup> percentile).

Supplementary Table 2. Effect of leptin replacement therapy on anthropometric and metabolic variables in the combined group of FPLD patients with severe and moderate hypoleptinemia.

Variable	All subjects (n=24)			P value
	0 mo	3 mo	6 mo	
Body Weight (kg)	66.6 ± 10.2	65.3 ± 10.4	64.3 ± 10.7	<0.0001
Body Fat (%)	17.8 ± 3.2	15.1 ± 4.1	15.7 ± 3.3	0.0003
Waist Circumference (cm)	81.5 ± 8.2	79.1 ± 6.5	79.4 ± 9.3	0.18
Hip Circumference (cm)	91.8 ± 5.0	90.3 ± 5.2	89.8 ± 5.5	<0.0001
Waist to Hip circumference ratio	0.89 ± 0.06	0.88 ± 0.05	0.88 ± 0.08	0.50
Chin Skinfold (mm)	11.5 ± 6.1	9.2 ± 4.5	9.6 ± 5.7	0.18
Subscapular Skinfold (mm)	17.1 ± 5.8	17.3 ± 7.0	16.0 ± 6.2	0.04
Abdominal Skinfold (mm)	12.4 ± 5.0	12.4 ± 4.7	9.9 ± 3.6	0.046
Hip Skinfold (mm)	11.8 ± 4.5	11.5 ± 3.3	11.1 ± 3.7	0.13
Skeletal muscle mass (kg)	29.8 ± 4.8	27.0 ± 2.3	29.7 ± 4.9	0.17
REE (kcal/d)	1421 ± 351	1278 ± 234	1244 ± 154	0.003
Serum leptin (ng/mL)	5.6 (4.5-7.6)	34.6 (15.2-64.9)	48.1 (25.2-68.0)	<0.0001
Total Cholesterol (mg/dL)	206 ± 59	193 ± 51	200 ± 94	0.31
Serum Triglycerides (mg/dL)	287 (214-259)	227 (169-392)	210 (139-333)	0.001
HDL Cholesterol (mg/dL)	33.7 ± 7.5	35.5 ± 7.4	34.7 ± 7.7	0.41
Liver Fat (%)	10.2 (5.6-23.7)	5.9 (2.3-14.6)	8.2 (1.6-19.2)	<0.0001
ALT (U/L)	28.7 ± 14.3	25.4 ± 15.4	26.8 ± 20.5	0.10
AST (U/L)	25.0 ± 8.5	22.4 ± 8.8	22.0 ± 10.7	0.01

P values in the last column represent the linear trend over Month 0, Month 3, and Month 6 using mixed model repeated measures analysis. ALT, alanine aminotransferase; AST, aspartate