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Bioactive leptin as a biomarker for monogenic obesity and insulin resistance in obese children and adolescents

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Rationale & Objectives

Leptin is satiety signal, which plays a role in both monogenic and polygenic obesity. Recently, two cases of children with early onset massive obesity due to bioinactive leptin in the face of normal total levels have been identified. Nevertheless, role of bioactive leptin as a biomarker for leptin gene mutations or insulin resistance (IR) was not systemically studied in children previously.

Aims & Objectives

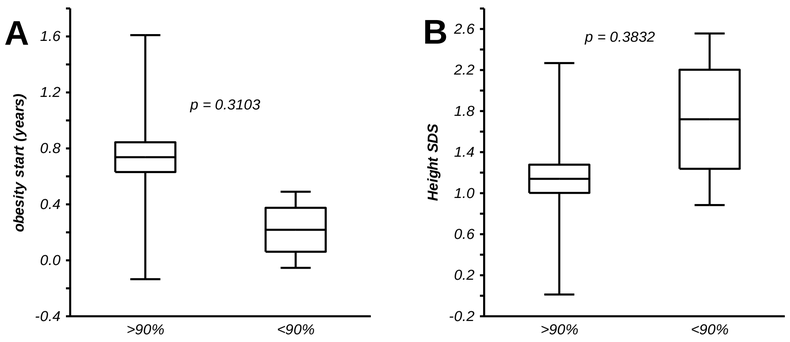
1. Identify leptin gene mutation carriers in a selected sample of obese children through decreased proportion of bioactive leptin,
2. Association of bioactive and immunoreactive leptin levels with parameters of insulin secretion/resistance in obese children and adolescents.

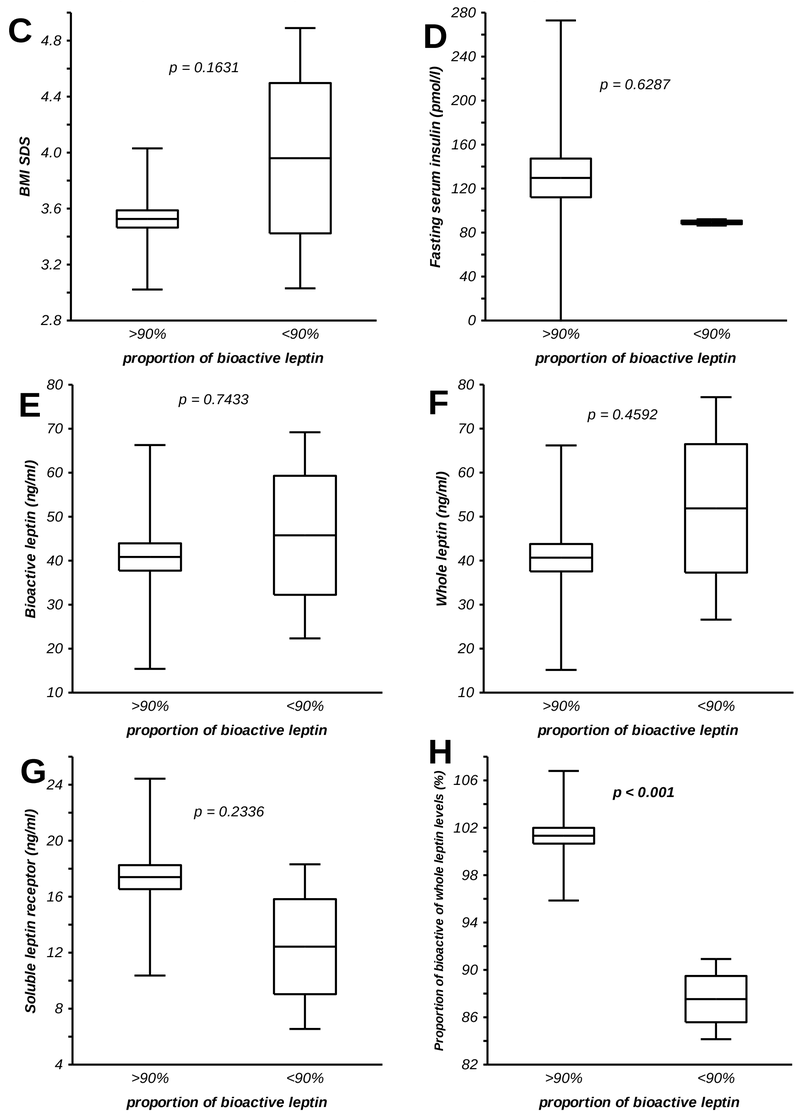
Research Design & Study Population

1. Cohort: Leipzig childhood obesity cohort (n=1204)
2. Selected n=70 (age 8.6 ± 4.9 years, BMI-SDS 3.5 ± 0.5) via inclusion criteria: age of obesity onset <3 years and maximum BMI SDS >3, exclusion criteria: syndromes, diabetes treatment (for insulin resistance study).
3. Laboratory measurements(by ELISA, IBL): bioactive, immunoreactive leptin and soluble leptin receptor in serum (whole cohort)
4. Monogenic study: Sanger sequencing of the leptin gene was performed in probands with proportion of bioactive/immunoreactive leptin <90% (<5th percentile).
5. Insulin resistance study: Associations of bioactive and immunoreactive leptin levels with selected parameters of insulin secretion/ resistance were calculated.

Results

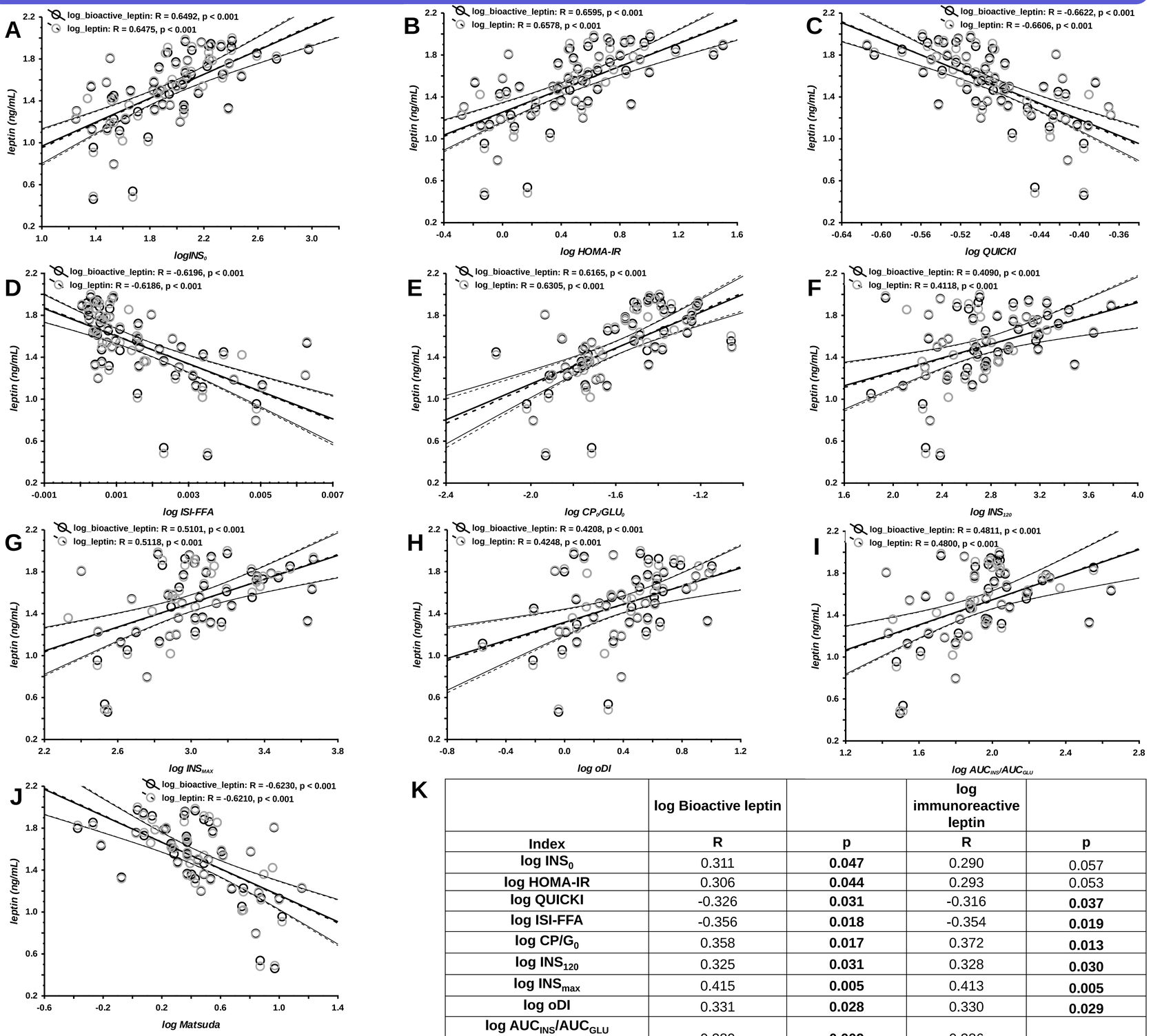
1. Bioactive and immunoreactive leptin levels in obese children





Only 3 children had proportion of bioactive to immunoreactive leptin less than 90% (5th percentile) (i.e. 83.6%, 89.3%, and 89.7%, respectively). There were no other significant differences in phenotype between these groups (A-H).
No mutations in the coding region of the leptin gene in the three selected probands were found.

2. Both bioactive and immunoreactive leptin correlate with IR indices



K

	log Bioactive leptin		log immunoreactive leptin	
Index	**R**	**p**	**R**	**p**
log INS_0	0.311	**0.047**	0.290	0.057
log HOMA-IR	0.306	**0.044**	0.293	0.053
log QUICKI	-0.326	**0.031**	-0.316	**0.037**
log ISI-FFA	-0.356	**0.018**	-0.354	**0.019**
log CP/G_0	0.358	**0.017**	0.372	**0.013**
log INS_{120}	0.325	**0.031**	0.328	**0.030**
log INS_{max}	0.415	**0.005**	0.413	**0.005**
log oDI	0.331	**0.028**	0.330	**0.029**
log AUC_{INS}/AUC_{GLU}	0.389	**0.009**	0.386	**0.010**
log Matsuda	-0.348	**0.021**	-0.344	**0.022**

Insulin resistance indices (correlated significantly with both bioactive and immunoreactive leptin levels (A-J).
In partial correlations (adjusted for sex, age, BMI SDS, pubertal status, and HbA1c), bioactive leptin correlated significantly with all of the selected indices and immunoreactive leptin with 8 of 10 indices. Nevertheless, the differences p-values are subtle (K).

Conclusions

This is the first study systematically using bioactive leptin as a biomarker for monogenic obesity and for insulin resistance indices in a sample of 70 obese children. In the monogenic part we have failed to identify any leptin gene mutation carriers based on the lowest bioactive leptin proportion. We have shown that the bioactive leptin levels correlated with selected insulin secretion and insulin resistance indices.

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