

The metabolic negative effect of gonadotropin-releasing hormone agonist therapy in childhood: is it short-term and reversible?

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Background - Published data on metabolic effects of gonadotropin-releasing hormone agonist (GnRHa) in childhood are still controversial, limited, and usually referred to a short-term follow-up period.

Objective - To longitudinally evaluate the effect of GnRHa therapy on body mass index (BMI), insulin sensitivity, and lipid profile in children with idiopathic central precocious puberty (CPP).

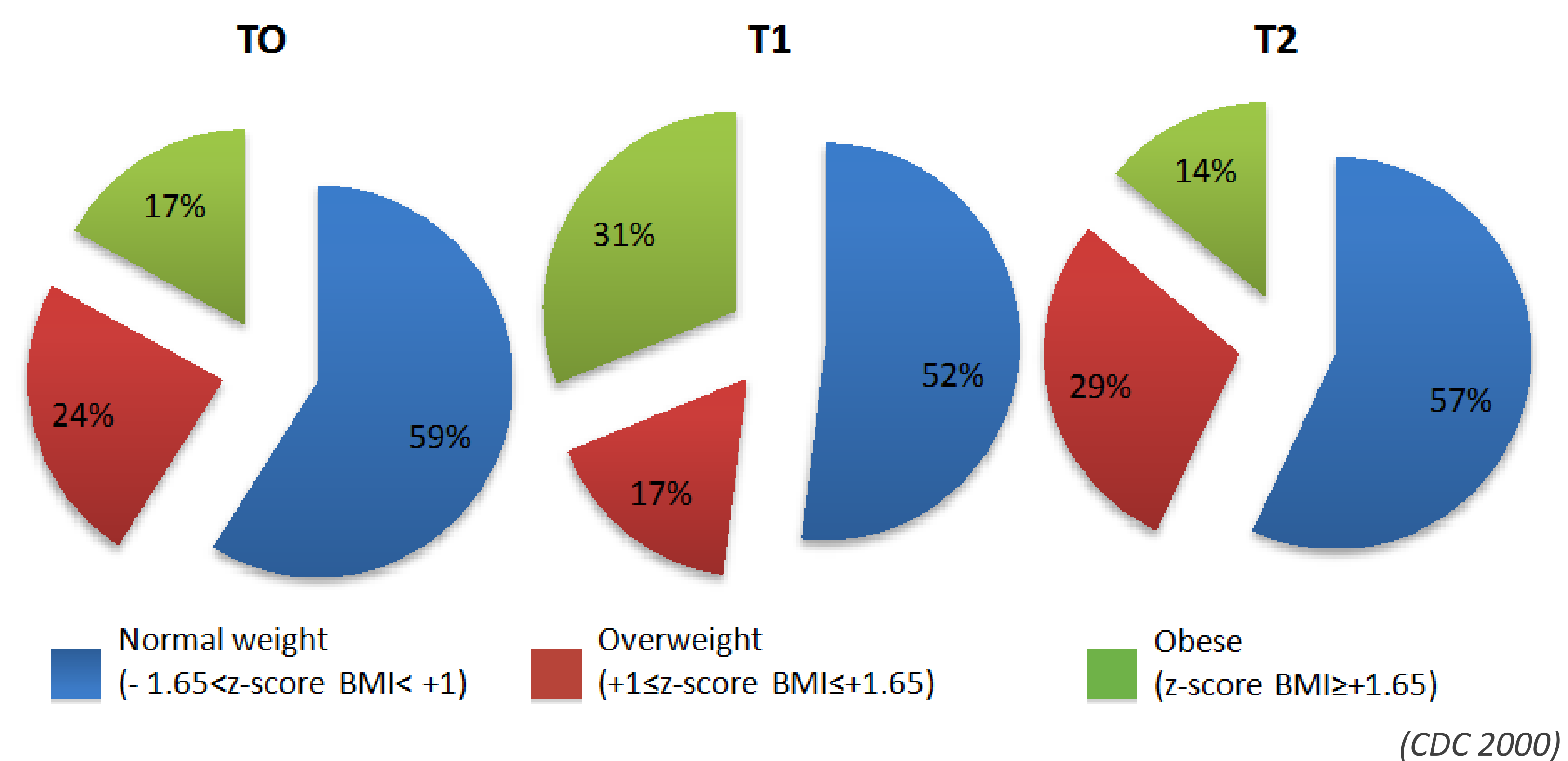
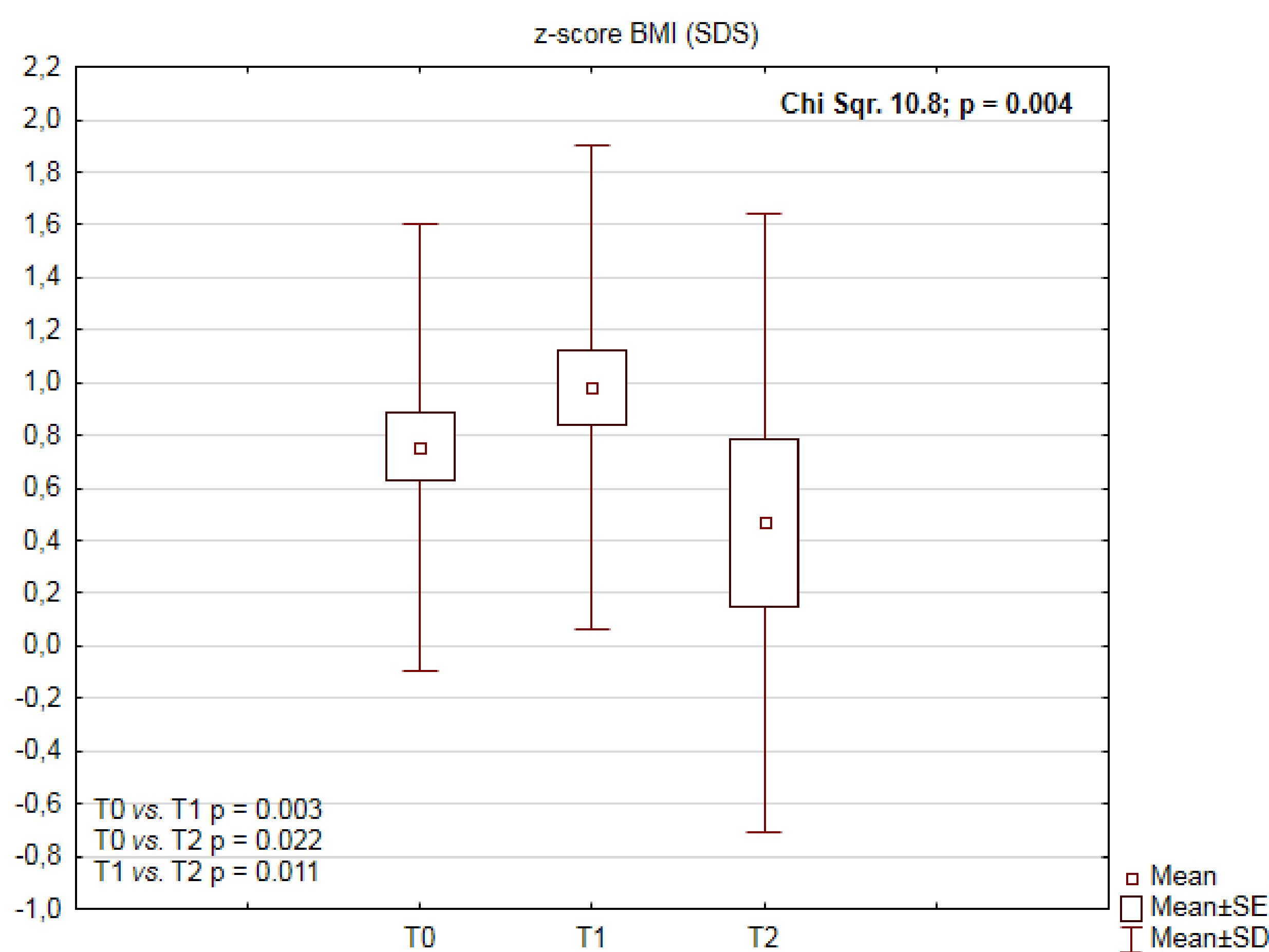
Methods – We determined...

What?	<ul style="list-style-type: none"> Auxological data (height, weight, BMI, and z-score BMI) Laboratory data [glycemia (G), insulin (I), G/I ratio, homeostatic model assessment index (HOMA-IR), total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides (TG), LDL-C/HDL-C, and TC/HDL-C ratios]
Who?	Forty-two children (age 7.70±0.80 years, 2 males; bone age 9.25±1.31 years) who were diagnosed with CPP and were treated with GnRHa (leuprorelin or triptorelin 3.75 mg, intramuscular injection every 28 days)
When?	<ul style="list-style-type: none"> T0 → before starting GnRHa therapy T1 → during treatment [mean time from T0 = 1.83±0.79 years (range 0.49-3.42 years)] T2 → after GnRHa discontinuation [mean time from last injection 5.40±1.73 years (range 2.21-8.49 years)]
How?	All data were checked using the Kolmogorov-Smirnov test: non-parametric statistical analysis (STATISTICA™ software, StatSoft Inc., Tulsa, OK, USA) was performed. All results are reported as the mean±SD. Longitudinal changes were analyzed using the Friedman ANOVA.

Results – Longitudinal changes...

1) BMI and z-score BMI

	T0	T1	T2	χ ²	p
Age (yrs.)	7.70±0.80	9.51±0.86	15.4±1.84	28.0	<0.0001
BMI (kg/m ²)	17.6±1.99	19.4±2.75	21.9±3.91	14.3	<0.001
z-score BMI (SDS)	0.76±0.85	0.98±0.92	0.46±1.17	10.8	0.004



Linear regression analysis identified age at diagnosis of CPP ($\beta=-1.08$, $p=0.01$) and z-score BMI at T1 ($\beta=0.81$, $p=0.001$) as main predictor factors for z-score BMI at T2.

2) Insulin sensitivity

	T0	T1	T2	χ ²	p
G (mg/dl)	83.7±10.1	85.0±10.9	75.6±19.6	8.46	0.014
I (μU/ml)	5.63±3.96	8.74±5.79	7.96±3.87	10.1	0.006
G/I ratio	20.4±10.3	14.1±10.6	9.70±5.38	10.8	0.004
HOMA-IR	1.02±0.74	1.87±1.17	1.41±0.82	6.0	0.049

As adjusted for pubertal stage [D'Annunzio G et al.], mean HOMA-IR values were slightly worse during GnRHa treatment (T1) than T0. However, despite the statistical significant increase we found at T1, data were mainly inside the normal range and improved after therapy was stopped (T2).

3) Lipid profile

	T0	T1	T2	χ ²	p
TC (mg/dl)	156.14±23.72	155.21±20.74	151.71±26.68	4.33	0.114
LDL-C (mg/dl)	86.44±21.32	88.68±21.29	81.14±22.48	2.33	0.311
HDL-C (mg/dl)	60.40±10.83	53.50±7.58	59.92±10.35	1.00	0.606
TG (mg/dl)	62.68±29.91	67.06±39.20	64.57±21.83	0.40	0.818
TC/LDL-C ratio	1.86±0.33	1.80±0.30	1.93±0.30	0.33	0.846
LDL-C/HDL-C ratio	1.44±0.38	1.68±0.50	1.41±0.41	2.33	0.311

Conclusions

- Our data confirm the direct and negative effect of the GnRHa *per se* on the z-score BMI
- The GnRHa seems to cause a slightly worsening of insulin sensitivity while lipid profile was not significantly modified by therapy

The metabolic negative effects of GnRHa is mild, is present only during the treatment, and is reversible upon discontinuation of therapy

References: Colmenares et al. *Int J Pediatric Endocrinol* 2014; 2014:5; D'Annunzio G et al. *Acta Biomed* 2009; 80:21; Karamizadeh Z et al. *Acta Med Iran* 2013; 51:41; Kim EY. *Korean J Pediatr* 2015; 58:1; Remsberg KE et al. *J Clin Endocrinol Metab* 2005; 90:2718; Sorensen K et al. *J Clin Endocrinol Metab* 2010; 95:3736.

