The Influences of Circulating Leptin, Kisspeptin, and Neurokinin B Levels to Precocious Puberty in Obese Girls

Min Jae Kang[1], Eun Young Kim[2], Yeon Joung Oh[1], Joon Woo Baek[2], Seung Yang[1], and Il Tae Hwang[1]

[1]Department of Pediatrics, Hallym University College of Medicine, Seoul, Korea

[2]Department of Pediatrics, Chosun Univertsity College of Medicine, Gwangju, Korea

INTRODUCTION

Candidate markers of pubertal onset

- **Leptin**: a major role in the metabolic gating of pubertal maturation
- **Kisspeptin**: an essential gatekeeper of puberty
- **Neurokinin B (NKB)**: coexpressed with kisspeptin in the arcuate nucleus and synchronizes the pulsatile secretion of kisspeptin.
- Metabolic status has a clear impact on the timing of puberty and leptin, kisspeptin, and NKB are influenced by energy balance.

The aim of this study

- To investigate the relationships of circulating leptin, kisspeptin, and NKB levels with precocious puberty in overweight/obese girls
- To evaluate the usefulness of these serum markers in the initiation of puberty.

SUBJECTS & METHODS

- The precocious puberty (PP) groups
  - 6≤ age < 9 years
  - Girls who presented with the complaint of early breast development
  - Confirmed with GnRH stimulation test (peak LH ≥ 5 mIU/mL) and bone age advancement (BA-CA ≥ 1 year)
- The control group
  - 6 ≤ age < 9 years
  - Consisted of healthy prepubertal girls
- Classification according to BMI z-score
  - Normal weight (5 percentile ≤ BMI z-score < 85 percentile)
  - Overweight (85 percentile ≤ BMI z-score < 95 percentile)
  - Obese (95 percentile ≤ BMI z-score)
- Definition of the groups
  - Gr 0: control_normal weight, n=38
  - Gr 1: PP_normal weight, n=85
  - Gr 2: PP_overweight/obese, n=54
- Chart reviews
  - Bone age: by Greulich and Pyle
  - Serum levels of IGF-1, IGFBP-3, basal LH/FSH/estradiol, peak LH/FSH (GnRH stimulation test)
- Biochemical Analysis
  - Leptin: ELISA kit (LDN Labor Diagnostika Nord GmbH & Co.)
  - Kisspeptin: EIA kit (Phoenix Pharmaceuticals, Inc.)
  - NKB: EIA kit (Peninsula Laboratories International, Inc.)
- Statistics
  - PASW Statistics 18.0 for Windows
  - Medcalc 15.8

RESULTS

1. Clinical characteristics of subjects

	Gr 0	Gr 1	Gr 2	P-value*
Age (years)[1]	8.1 (7.3~8.6)	8.6 (8.2~8.9)	8.7 (8.3~8.9)	<0.001
Bone age (years)[1]	7.0 (6.9~7.9)	10.5 (10.0~11.0)	10.5 (10.0~11.0)	<0.001
BA-CA (years)[1]	-0.7 (-1.3~0.3)	1.8 (1.5~2.3)	2.0 (1.4~2.6)	<0.001
BMI z-score[1,2]	-0.20 (-0.98~0.49)	0.28 (-0.24~0.76)	1.41 (1.2~1.72)	<0.001
IGF-1 (ng/mL)[1]	157 (126~211)	296 (246~355)	320 (247~374)	<0.001

Data are expressed as median and interquartile ranges.
* By Kruskall-Wallis test
[1] Gr 0 vs. Gr 1, by Mann-Whitney U test
[2] Gr 1 vs. Gr 2, by Mann-Whitney U test

2. GnRH stimulation test in PP subjects

	Gr 0	Gr 1	Gr 2	P-value[2]
Basal LH (mIU/mL)	0.6 (0.4~0.7)	0.8 (0.5~1.7)	0.7 (0.3~1.6)	0.364
Basal FSH (mIU/mL)[1]	1.4 (0.5~2.7)	2.5 (1.8~3.8)	2.6 (1.9~4.2)	0.617
Basal estradiol (pg/mL)[1]	0.5 (0.1~3.6)	6.3 (0.1~11.7)	6.6 (2.9~10.7)	0.450
Peak LH (mIU/mL)	Not done	7.9 (6.5~13.8)	10.9 (6.5~16.5)	0.257
Peak FSH (mIU/mL)	Not done	15.4 (11.9~18.5)	15.8 (12.8~18.9)	0.470

3. Serum levels of biochemical markers

	Gr 0	Gr 1	Gr 2	P-value*
Leptin (ng/mL)[1,2]	2.2 (1.6~3.0)	3.8 (2.6~4.7)	4.8 (3.2~8.0)	<0.001
Kisspeptin (ng/mL)[2]	0.57 (0.51~0.69)	0.57 (0.48~0.65)	0.64 (0.52~0.72)	0.096
NKB (pg/mL)	62.5 (51.3~74.3)	57.5 (39.0~71.3)	62.3 (50.8~73.1)	0.182

4. ROC curves of serum markers

Leptin
AUC 0.754
95%CI: 0.664-0.845

IGF-1
AUC 0.927
95%CI: 0.886-0.969
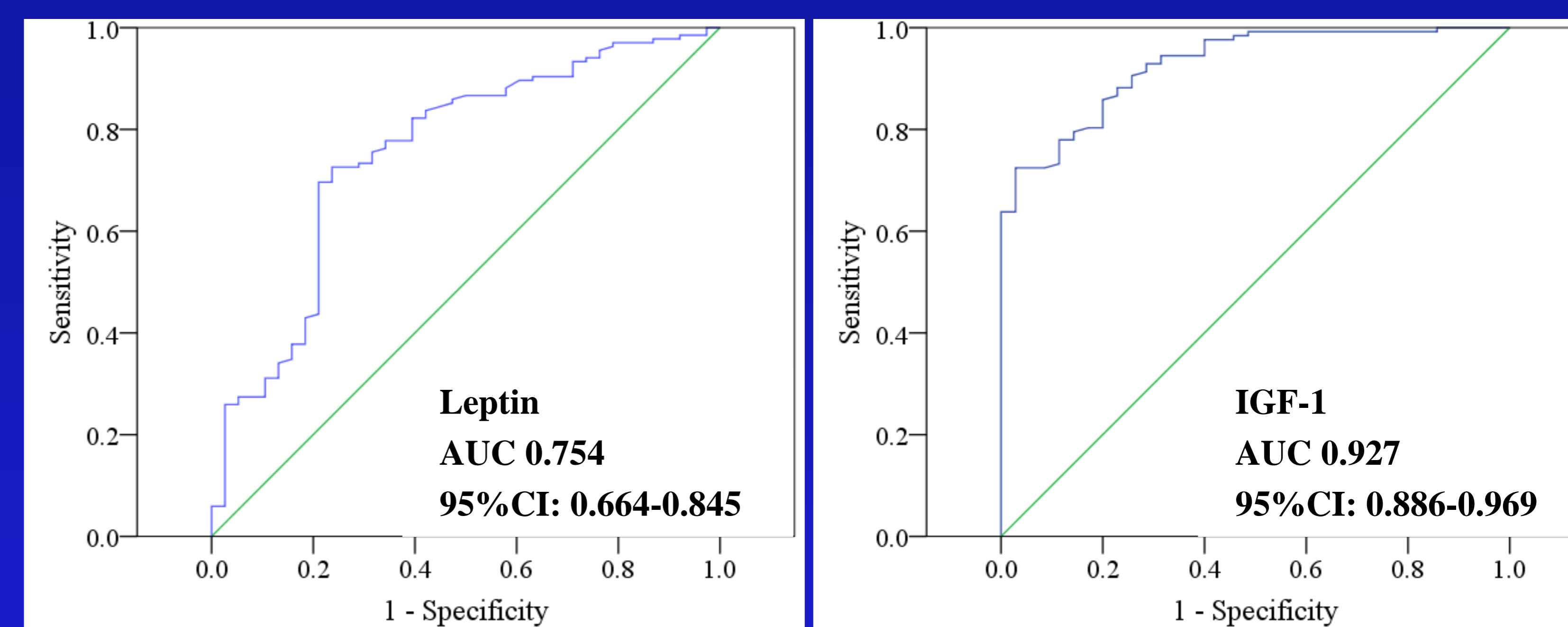
5. Prediction of PP by serum markers

	Odds ratio	95% C.I.	P-value
Leptin	1.398	0.794-2.461	0.245
IGF-1	1.035	1.009-1.061	0.007
Basal FSH	1.364	0.903-2.060	0.141

CONCLUSIONS

1) Higher level of serum leptin in overweight/obese girls with PP compared to normal controls confirmed the role in the regulation of puberty.
2) Yet, although it is clear that the effects of leptin on pubertal onset are positive, the commercialization in clinical practice as a diagnostic marker for PP compared to other established hormones might be difficult.
3) Aside from their serum levels, autocrine and paracrine interactions of kisspeptin and NKB may play a more important role in the true activation of hypothalamic-pituitary-gonadal axis.

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Min Jae

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