# Developmental regulation of obestatin and adropin in Prader-Willi syndrome and non-syndromic obesity: associations with weight, BMI-z, HOMA-IR, and lipid profile

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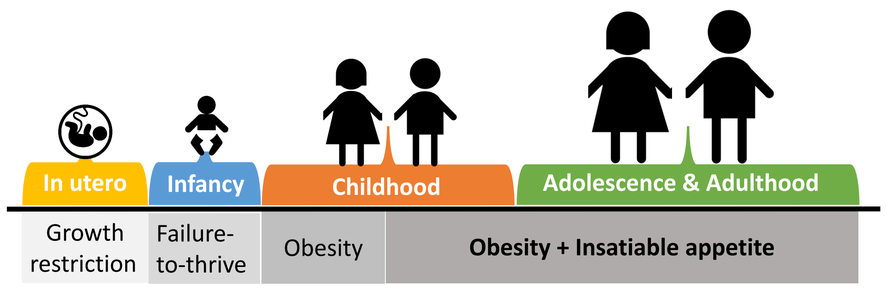
## INTRODUCTION

- Prader-Willi Syndrome (PWS) is a genetic disorder characterized by distinct nutritional phases[1].




- The peptides obestatin and adropin are thought to regulate glucose and lipid metabolism and weight gain in adults[2,3,4]. However, the roles of obestatin and adropin in the regulation of weight and glucose and lipid metabolism in PWS and non-syndromic pediatric obesity are poorly understood.

## OBJECTIVES

1. To compare the concentrations of obestatin, ghrelin to obestatin ratio, and adropin in infants and children with PWS and age- and BMI-z matched controls.

2. To explore the associations between obestatin and adropin and other energy-regulating hormones.

## METHODS

- **Study design:** Secondary analysis of cross-sectional studies on hormonal and metabolic characteristics of individuals with PWS[5,6].

- **Participants:** Infants and children with PWS and controls of similar age and BMI-z score were recruited from clinics at Duke University.

PWS (n=21) | Controls (n=17)

PWS (n=14) | Controls (n=14)

- **Assays:** Plasma fasting obestatin (Yanaihara Institute, Shizuoka, Japan) and adropin (Peninsula Laboratories, San Carlos, CA) were measured in duplicate using ELISAs. Data from additional hormones were included here[5,6].

- The ratio of ghrelin to obestatin was calculate as a measure of differential processing of preproghrelin.

- **Statistics analysis:** Data are presented as median and interquartile range (25th, 75th). Comparisons were performed using Independent Student's t-tests, after logarithmic or inverse transformation.

- Pearson's (r) correlation coefficient was used to evaluate correlations between obestatin and adropin levels, and with other metabolic biomarkers.

## RESULTS

**Table 1. Characteristics of infants**

| Variables | PWS infants (n = 21) | Control infants (n = 17) | P-value[b] |
|---|---|---|---|
| **Age (months)[a]** | 15.5 (10.7, 31.9) | 27.3 (10.4, 45.6) | 0.82 |
| **Sex** | 12 male, 9 female | 8 male, 9 female | N/A |
| **Weight for age z-score** | -0.99 (-1.71, 0.98) | 0.16 (-0.46, 0.94) | 0.09 |
| **PWS subtype** | | | |
| **Deletion** | 11 (52.4%) | - | - |
| **UPD** | 9 (42.9%) | - | - |
| **Undetermined** | 1 (4.7%) | - | - |
| **GH treatment** | 18 (85.7%) | - | - |
| **Ghrelin (pg/mL)[a]** | 2190.0 (1593.5, 3283.5) | 1980.0 (1644.6, 2240.5) | 0.06 |
| **Leptin (ng/mL)[a]** | **6.29 (3.50, 7.09)** | 3.47 (2.64, 5.13) | **0.01** |
| **Insulin (µIU/mL)[a]** | **7.66 (6.29, 10.20)** | 5.94 (4.45, 7.36) | **0.01** |
| **Glucose (mg/dL)[a]** | 85.20 (76.40, 88.80) | 81.00 (77.80, 85.00) | 0.99 |
| **HOMA-IR[a]** | **1.60 (1.29, 2.13)** | 1.15 (0.93, 1.56) | **0.03** |

**Table 2. Characteristics of children**

| Variables | PWS children (n = 14) | Control children (n = 14) | P-value[b] |
|---|---|---|---|
| **Age (years)** | 11.4 (7.1, 14.9) | 12.0 (10.3, 14.6) | 0.38 |
| **Sex** | 9 male, 5 female | 6 male, 8 female | N/A |
| **Body mass index z-score** | 2.2 (1.5, 2.6) | 2.3 (1.8, 2.7) | 0.87 |
| **PWS subtype** | | | |
| **Deletion** | 9 (64.3%) | - | - |
| **UPD** | 4 (28.6%) | - | - |
| **Undetermined** | 1 (7.1%) | - | - |
| **GH treatment** | 9 (64.3%) | - | - |
| **Ghrelin (pg/mL)** | **1468.5 (1133.4, 1659.1)** | 836.7 (712.9, 918.6) | **< 0.0005** |
| **Leptin (ng/mL)** | 31.45 (12.78, 48.84) | 32.24 (14.92, 54.71) | 0.86 |
| **Insulin (µIU/mL)** | 13.49 (10.02, 29.48) | **23.20 (17.08, 35.50)** | **0.03** |
| **Glucose (mg/dL)** | 87.75 (80.88, 101.69) | 94.88 (88.25, 99.56) | 0.52 |
| **HOMA-IR[a]** | 3.20 (2.38, 5.80) | **5.11 (4.10, 8.92)** | **0.02** |

Values are median (25th percentile, 75th percentile) unless otherwise indicated. [a] Variables were transformed logarithmically for statistic analysis, but present here as raw values. [b] P-values determined using independent t-test (Pearson). Statistically significant differences are in bold type ($p \leq 0.05$). GH, growth hormone; HOMA-IR, homeostatic model assessment-insulin resistance; PWS, Prader-Willi syndrome, N/A: not applicable; UPD, uniparental dysomy.

### OBJECTIVE 1 – Obestatin, ghrelin to obestatin ratio, and adropin concentrations in infants and children with PWS and controls

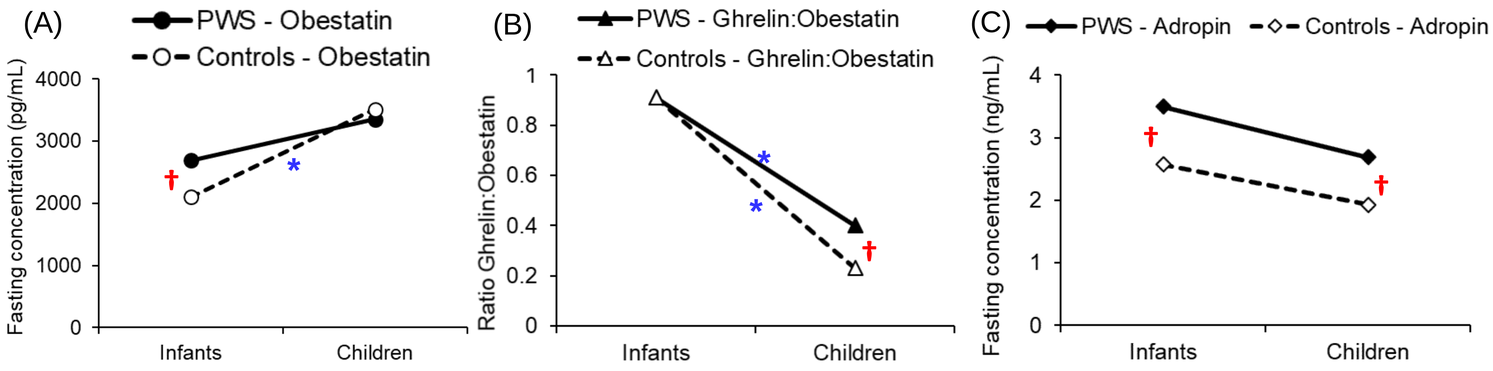


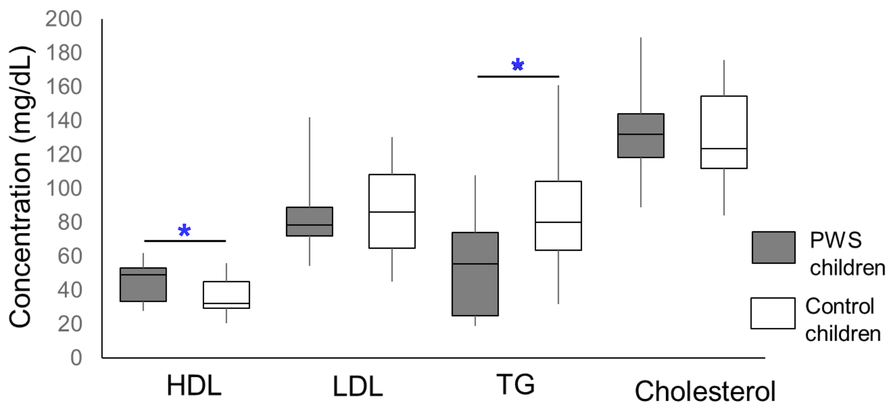

**Figure 1:** Median changes in fasting (A) obestatin concentrations, (B) ghrelin to obestatin ratio, and (C) adropin concentrations during development in Prader-Willi syndrome (PWS) and controls.

* Statistically significant differences between infants and children ($p \leq 0.05$). † Statistically significant differences between PWS and controls ($p \leq 0.05$).

- Growth hormone treatment had no effects on obestatin or adropin in PWS children.

### OBJECTIVE 2 – Correlation between obestatin, adropin and other energy-regulating hormones

- Obestatin was significantly correlated with adropin in all groups (r=0.54-0.75, all $p \leq 0.05$).
- Adropin correlated with fasting glucose in children with PWS (r=0.78, $p<0.01$)
- Obestatin correlated with BMI z-score (r=0.81, $p<0.0005$), leptin (r=0.66; p=0.01), and HOMA-IR (r=0.69, p=0.01) in control children.




- In control children, obestatin was negatively correlated with HDL (r=-0.57, p=0.03) and positively with TG (r=0.54, p=0.05).

**Figure 2.** Box plots showing the differences of high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), and total cholesterol between children with PWS (n=14) and controls (n=14). Data were not available for infants. * $p \leq 0.05$ by Independent t-test.

## CONCLUSIONS

- Infants with PWS had higher obestatin concentrations than control subjects of similar age and BMI.
- Fasting adropin concentrations in older PWS children were related to glucose levels in the higher (but normal) range, but not with other markers of metabolism or insulin resistance.
- Changes in the ratio of ghrelin to obestatin during childhood suggest developmental changes in the processing of preproghrelin and differential processing in PWS and control subjects.

**REFERENCES: 1.** Miller JL et al. Nutritional phases in Prader-Willi syndrome. *Am J Med Genet Part A* 2011; 155: 1040-1049. **2.** Pradhan G et al. Obestatin stimulates glucose-induced insulin secretion through ghrelin receptor GHS-R. *Sci Rep*. 2017;7(1):1-10. **3.** Gao S et al. Therapeutic effects of adropin on glucose tolerance and substrate utilization in diet-induced obese mice with insulin resistance. *Mol Metab*. 2015;4(4):310-324. **4.** Stein LM et al. Adropin acts in brain to inhibit water drinking: potential interaction with the orphan G protein-coupled receptor, GPR19. *Am J Physiol - Regul Integr Comp Physiol*. 2016;310(6):R476-R480. **5.** Haqq AM et al. The metabolic phenotype of Prader-Willi syndrome (PWS) in childhood: Heightened insulin sensitivity relative to body mass index. *J Clin Endocrinol Metab*. 2011;96(1):225-232. **6.** Haqq AM et al. Ghrelin concentrations in Prader-Willi syndrome (PWS) infants and children: changes during development. *Clin Endocrinol (Oxf)* 2008; 69: 911-920.

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