CIRCADIAN RHYTHM OF SALIVARY CORTISOL IN OBESE CHILDREN WITH CLINICAL SIGNS OF HYPERCORTISOLISM

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INTRODUCTION
- The increased prevalence of childhood obesity (OB) is nowadays associated to a greater referral of obese children to investigate endocrine diseases causing or contributing to OB [1].
- Weight gain, associated to delayed growth, is the classical presentation of true hypercortisolism (HF) in children who are still growing [2]. In older children, the clinical features may overlap with those observed in exogenous Cushing [3].
- The loss of the cortisol (F) nocturnal nadir constitutes the biochemical hallmark of HF regardless of its cause. Late night salivary F is easy to perform in children, however, the cut-off of 4 nmol/L, suggestive of Cushing Syndrome (CS), was obtained in adults [3,4].
- The circadian rhythm (CR) of salivary cortisol may provide useful information on HF in obese children with clinical signs of F overproduction.

AIMS
- To describe possible disturbances in the circadian rhythm of salivary cortisol in obese children with clinical signs of hypercortisolism.
- To evaluate the 99th centile of SAF at night obtained in obese children as a potential cut-off for assessment of hypercortisolism states in pediatric settings.

SUBJECTS & METHODS
Design: Cross-sectional, age-matched, observational, prospective study.
Obese (OB) Inclusion criteria-BMI 99th centile and clinical signs suggestive of HF.
- Concomitant weight gain and delayed growth or.
- Obesity associated to ≥2 of the following: moon face, red striae, headache, hypertension, hirsutism, acanthosis nigricans, insulin resistance, acanthosis nigricans, ovari안 dysfunction, dyslipidemia.
- Evaluation of criteria: Syndrome obesity, Cushing Syndrome (CS).
- Clinical follow up of at least 2 years and appropriate biochemical tests.

CS (n=62)
OB non-CS (n=42)

SAF8 (nmol/L)

Figure 1: Circadian Rhythm of Salivary Cortisol

Study children (n=143)

Table 2: Auxological and biochemical features of the study groups

<table>
<thead>
<tr>
<th>Gender (F/M)</th>
<th>NW (n=73)</th>
<th>OB non-CS (n=62)</th>
<th>CS (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA (years)</td>
<td>10.4 (2.2 – 16.0)</td>
<td>11.9 (2.5 – 16.0)</td>
<td>14.1 (7.8 – 16.9)</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>53/11/3</td>
<td>53/11/3</td>
<td>53/11/3</td>
</tr>
<tr>
<td>SAF8 (nmol/L)</td>
<td>11.0 (5.1 – 24.7)</td>
<td>6.9 (3.0 – 15.1)***</td>
<td>31.9 (8.6 – 43.9)</td>
</tr>
<tr>
<td>SAF8 (nmol/L)</td>
<td>2.0 (2.0 – 4.6)</td>
<td>2.0 (2.0 – 4.6)</td>
<td>18.9 (6.0 – 81.0)</td>
</tr>
<tr>
<td>ACh (nmol/L)</td>
<td>8.1 (2.8 – 20.4)</td>
<td>4.6 (1.3 – 12.2)***</td>
<td>10.5 (4.7 – 14.4) Δ</td>
</tr>
<tr>
<td>RCh (%)</td>
<td>78 (53 – 91)</td>
<td>66 (31 – 86)***</td>
<td>41 (26 – 49)κ</td>
</tr>
</tbody>
</table>

Data are expressed as the median (3P - 97P); *** p< 0.0001 versus NW (t-test); Δ in 4/8 CS patients. CA: Chronological age; F: females; M: males

RESULTS
- Circadian rhythm of cortisol was preserved in NW and obese children with clinical signs of hypercortisolism (in whom hypothalamic-pituitary-adrenal axis disorders were ruled-out), by using simple and non-invasive saliva samples at 8 and 23 hs under standardized procedures.
- SAF23 cut-off of 5.0 nmol/L by ECLAIA method is in range accordance with the one recommended threshold of Endocrine Society Guidelines (4 nmol/L) that was obtained by gold standard tandem mass spectrometry [3,4].
- In children with Cushing Syndrome, SAF23 was always higher than our proposed cut-off value that could be indicative of hypercortisolism in pediatrics and should be further confirmed according to clinical, biochemical and images studies.
- Obesity is a stressor and therefore, it may influence circadian rhythms. Lower SAF8 in obese could not be exclusively explained by increasing BMI. SAF8 reflects the biologically active F fraction of cortisol and therefore, SAF8 differences between NW and OB non-CS are not associated to binding proteins status. The abnormal lipid profile observed in 80% of our obese non-CS cohort may suggest that other biomarkers of chronic inflammation could also induce changes in cortisol secretion, metabolism and/or excretion.

CONCLUSIONS

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REFERENCES
2. Lodish MB et al. Endocrinol Metab Clin North Am 2018

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Figure 2: SAF8 versus BMI

Table: SAF8 versus BMI

- BMI-SDS was the strongest independent variable associated to lower SAF8 (multiple regression study, figure 2).
- Differences in SAF8, ACh and RCh between NW and OB non-CS were maintained after BMI-SDS adjustment (p<0.001).

A significant proportion of OB non-CS (17/62) presented RCh=53% (3P centile in NW) as compare to NW (17/73), Fisher test p<0.001.

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