Evaluation of allostatic load as a marker of chronic stress in children: the importance of the excess of weight.

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Background

Chronic exposure to stressful stimuli, is referred to as *allostatic load* (AL), and results in "wear and tear" of the adaptive regulatory systems resulting in biological alterations that weaken stress adaptive processes and increase disease susceptibility. Chronic dietary imbalances, for example as observed in western diets rich in fats and refined sugars that lead to excessive weight gain, may affect physiological performance promoting chronic low-inflammation that is detrimental for both the physical and mental status. The consequential increase in pro-inflammatory cytokines, such as IL-6, leads to increased hypothalamic-pituitary-adrenal (HPA-) axis activity and promotes chronic stress. In this study, we measured AL scores in a caucasian pediatric population, in order to define a correlation between cumulative biological dysregulation and excess weight.

Patients and methods

We consecutively enrolled 164 caucasian children and adolescents (79F/85M) aged 11.89 ± 3.89 yrs. The subjects were referred to our institution for auxological evaluation or obesity by their general practitioner or by their primary care pediatric consultant, between October 2017 and March 2018.
According to body mass index (BMI) cutoffs and age-sex percentiles subjects were classified as normal for weight: BMI<75th percentile, overweight: BMI 75-95th percentile or obese: BMI>95th percentile.
We used 16 biomarkers to create an AL summary score. We included 1) markers of cardiovascular and metabolic activity (BMI, waist circumference (WC), waist to height ratio (WHtR), blood pressure, fasting lipid and blood glucose levels, insulin resistance, transaminases and homocysteine levels); 2) inflammatory markers (calprotectin, IL-6 and PCR); 3) marker of stress (serum cortisol level).
For each biomarker, a dichotomous variable was constructed in which 0 and 1 respectively correlated with values under the clinical cutoffs for age and gender and those in the pathological clinical range. Risk factors were summed to calculate a total AL score and the population median for the sum of the dysregulated components in our sample was 4. All patients who scored less than 4 were considered low AL and vice versa for all the others.
We used this dichotomous scoring system to achieve a well matched sample size and consequently obtain more statistical power.

Results

Based on the BMI percentile threshold, 49 of the 164 (29.88%) enrolled patients were normal for weight and 115 (70.12%) were overweight or obese. Tables 1 and 2 show the biomarker distributions utilized for the AL summary score, and the number of dysregulated values used to generate the score.

Table 1. Parameter distributions used to create the allostatic load (AL) summary score.

Parameters	Absent	Present
Body mass index > 75th percentile	49 (29.88%)	115 (70.12%)
Waist circumference> 95th percentile	57 (34.76%)	107(65.24%)
Waist to height ratio >0.5	68 (41.46%)	96 (58.54%)
Systolic blood pressure≥95th percentile	144 (87.8%)	20 (12.2%)
Diastolic blood pressure> 95th percentile	153 (93.29%)	11 (6.71%)
High density lipoprotein (HDL) cholesterol<5th percentile	113 (81.09%)	31 (18.91%)
Total cholesterol >95th percentile	149 (90.85%)	15 (9.15%)
Triglycerides>95th percentile	152 (92.68%)	12 (7.32%)
Fasting blood glucose>100 mg/dl	161 (98.17%)	3 (1.83%)
HOMA-IR>95th percentile	136 (82.92)	28 (17.18%)
Pathological ALT (nv 11-39 mU/ml) and AST (nv 11-34 mU/ml) and/or GGT (nv 11-53 mU/ml)	162 (98.78%)	2 (1.22%)
Homocysteine (nv 5-13.9 µmol /L)	132 (80.48%)	32 (19.52%)
PCR>0.5 mg/L	145 (88.41%)	19 (11.59%)
Pathological IL-6 (nv 0-12.5 pg/ml)	160 (97.56%)	4 (2.44%)
Pathological calprotectin (nv 0.3-1.6 µg/ml)	75 (45.73%)	89 (54.27%)
Elevated morning cortisol level (nv 4.3-22.4 µg /ml)	163 (99.39%)	1 (0.61%)

nv: normal value; HOMA-IR: homeostasis model assessment for insulin resistance.

Table 2. Number of dysregulated components used to create the allostatic load summary score.

Number of AL parameters	Percentage of patients (%)	Cumulative percentage of patients (%)
0	14.02	14.02
1	12.80	26.83
2	4.27	31.10
3	15.24	46.34
4	15.24	61.59
5	17.68	79.27
6	11.59	90.85
7	5.49	96.34
8	1.22	97.56
9	1.83	99.39
10	0.61	100

A high AL score was observed in 88/164 subjects (53.65%), without significant differences between genders (p=0.07) or pubertal status (p=0.10).
As reported in Table 3, report the correlations between AL, clinical data and metabolic/ hormonal parameters. Subjects with a significantly higher BMI (p<0.001), WC and WC/HtR (p<0.001), triglycerides (p=0.002), fasting blood glucose (p=0.03), GGT (p=0.01), PCR (p=0.01), calprotectin (p<0.01) insulin resistance (p<0.001), systolic (p<0.0019 and diastolic blood pressure (p=0.001) values as well as lower HDL cholesterol (p=0.002) levels had a higher AL score.
A significant correlation between high AL score and excess weight was observed (87/88 of patients with pathological BMI had a high AL score vs 1/49 in normal weight subjects p<0.001). It was also noted that increasing BMI correlated with increased cumulative biological dysregulation (p< 0.001).

Table 3. Correlation between allostatic load (AL), clinical data and biochemical/hormonal parameters.

Parameters	Low AL (<4)	High AL (≥4)	p_value
Height (cm)	146.59±22.82	150.58±15.47	0.18
Weight (Kg)	45.22±17.02	59.92±17.65	<0.001
Body Mass Index (kg/m^2)	21.23±11.88	25.8±3.88	<0.001
Waist circumference (cm)	72.47±10.78	84.98±9.71	<0.001
Waist to height ratio >0.5	0.34±0.04	0.55±0.52	<0.001
Pubertal status*			
Tanner stage 1	30 (39.47)	25 (28.41)	
Tanner stages 2-3	40 (52.63)	55 (62.50)	
Tanner stages 4-5	6 (7.80)	8 (9.09)	0.10
Systolic blood pressure (mmHg)	106.54±9.84	112.82±10.15	<0.001
Diastolic blood pressure (mmHg)	66.53±8.26	70.57±8.04	0.001
High density lipoprotein cholesterol (mg/dL)	55.73±11.32	49.61±11.02	0.002
Total cholesterol (mg/dL)	152.87±22.95	160.17±29.55	0.14
Triglycerides (mg/dL)	60.04±29.2	80.98±41.8	0.002
Fasting blood glucose (mg/dL)	72.89±10.57	76.71±2.04	0.03
HOMA-IR	1.46±1.13	2.57±1.96	<0.001
Aspartate Aminotransferase (mU/ml)	23.08±5.45	23.33±13.26	0.9
Alanine Aminotransferase (mU/ml)	14.84±5.36	17.56±9.16	0.06
Gamma-Glutamyl Transferase (mU/ml)	11.83±4.64	14.58±6.34	0.01
Homocysteine (µmol /L)	12.68±7.52	13.11±3.14	0.67
PCR (mg/L)**	.04 (.02-.1)	.16 (.03-.48)	0.01
IL-6 (pg/ml)**	1.97 (.8-5.7)	2.83 (1.51-5.77)	0.23
Calprotectin (µg/ml)**	1.1 (.8-1.9)	2.6 (1.7-4.3)	<0.001
Cortisol (µg /ml)	8.20±3.97	8.85±4.89	0.5

AL= allostatic load
*data are expressed as the number of patients (percentage)
**data are expressed as the median (interquartile range)

Conclusions

In conclusion, we describe a correlation between cumulative biological dysregulation and excess weight in children and adolescents, suggesting that AL could be a useful index of health risk in the pediatric population offering a valuable measure to predict complications in obese children and promote early tailored interventions to enhance their quality of life.