Association between obesity and autonomic nervous system activity in children

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Abstract

Introduction: Obesity is one of the most prevalent chronic diseases in childhood, being an important public health issue. Excess weight has been associated with autonomic dysfunction but the evidence in children is scarce. Therefore, this study aimed to assess the effect of overweight and obesity on the autonomic nervous system activity in children. Because dysfunction of the autonomic nervous system (ANS) may lead to development or stabilization of obesity and is related with cardiovascular mortality, the study of ANS function in obesity is of significant clinical interest. Studies of ANS function in obese children have been limited to investigations of cardiac autonomic function through analysis of heart rate variability. These studies have generally revealed a reduced parasympathetic activity. It remains unclear, whether abnormalities of ANS can be found in the sympathetic nervous system, and outside of the cardiac autonomic nerve function in overweight and obese adolescents and children.

Methods to measure autonomic nervous system function outside the cardiac system include sympathetic skin response (SSR) and quantitative pupillography. SSR is a simple, reproducible method to assess the polysynaptic reflex loop which comprises diverse afferents, a common efferent pathway through the spinal cord, pre- and postganglionic sympathetic fibres, and perspiratory glands as effectors. SSR may be affected by pathology of both the central sudomotor and peripheral nervous systems. In obese adults, SSR is not distorted. However, SSR has, to the best of our knowledge, not been assessed previously in overweight or obese children. Autonomic innervation of the pupil is controlled by both the sympathetic and the parasympathetic nervous systems. Pupillary response may be quantified by means of direct pupillography by measuring the pupil diameter in the dark (PDD) and subsequent exposure to a light stimulus. Pupil size and re-dilation velocities (early and late) are thought to reflect sympathetic pupillary modulation while latency light reflex, amplitude and constriction velocity are controlled by parasympathetic activity. PDD and amplitude, velocity of pupillary constriction and latency of pupillary response and of re-dilation following light stimulation are impaired in diabetic patients and may represent the earliest manifestations of peripheral autonomic neuropathy. In diabetic adolescents the PDD and pupillary dilation are significantly decreased compared to healthy peers and the degree of the impairment correlates with the duration of the disease. It has not previously been studied that how pupillary function is influenced by obesity.

Methods: Data were collected from a cross sectional study including 916 children (7 to 12 years), from 20 primary schools in Porto, Portugal. Anthropometric measurements and bioelectrical impedance analysis were performed to assess body mass index (BMI) and characterize body composition - body fat percentage, body fat mass and total body water. BMI was classified according to age- and sex-specific percentiles defined by the World Health Organization, the US Centers for Disease Control and Prevention and the International Obesity Task Force. Pupillometry was performed to evaluate autonomic activity. Mann-Whitney, the chi-square, and Kruskall-Wallis tests were used as appropriate.

1. Clinical and anthropometric data
A thorough medical history was obtained, and a physical assessment was performed in all participants to exclude any concomitant disease. For anthropometric measurements, all children were assessed barefoot and only wearing light underwear. Body height of those children was measured by the digital stadiometer Dr. Keller III. Body weight was determined by a digital scale. Body mass index (BMI) was calculated by the formula: weight

in kilograms divided by the square of height in meters. The BMI-SDS provides a normalized measurement for the degree of overweight or obesity. By applying the LMS method, it is assumed that BMI data of each age group are normally distributed. A cut off ≥1.28 SDS (90^{th} centile) classifies overweight and a cut off ≥1.88 SDS (97^{th} centile) classifies obesity in children. Pubertal stage was assessed according to Tanner stages 20.

In obese children, fasting plasma glucose, fasting insulin, transaminases (ALAT, ASAT, GGT), uric acid, triglycerides, cholesterol, HDL-cholesterol and LDL-cholesterol levels were measured by a certified laboratory. An oral glucose tolerance test (OGTT) was performed to exclude impaired glucose metabolism. Blood samples for the OGTT were collected at 0, 30, 60, 90 and 120 minutes after a glucose load of 1.75 g/kg body weight (maximum of 75g glucose). Impaired glucose tolerance was defined as a glucose level >7.8 mmol/l 120 minutes after the glucose load 18. Insulin sensitivity was determined by applying insulin resistance (HOMA-IR) for the homeostasis model assessment. HOMA-IR was calculated using the equation HOMA-IR=fasting insulin (µU/mL) x fasting glucose (mmol/l)/22.5. (21). Blood pressure was obtained by the arithmetic mean of three single measurements by a certified device in the supine position after a rest period.

2. Autonomic nervous function

For the classification of autonomic nervous function (sympathetic/parasympathetic activity), 3 different methods were applied. Measurements were performed during afternoon between 1 and 3 pm, following a rest period of 15 minutes.

2.1. Heart rate variability (HRV): To screen for cardiac autonomic function, HRV was measured in the resting position and following deep breathing via the computer-based system ProScicard. Measurements were performed over a five minute period, and the time-domain and frequency-domain indices of HRV were analysed: root mean square of successive differences (RMSSD), power spectral analysis in the low frequency spectrum ln(LF); (0.05–0.15 Hz) and in the high frequency spectrum ln(HF); (0.15–0.5 Hz) and the low frequency/high frequency ratio (ln(LF/HF) ratio) were calculated. Measurements under deep breathing were performed over a period of 110 heart beats and a stable respiratory frequency of 6 cycles per minute. The ratio of the longest RR interval during expiration to the shortest interval during inspiration (E/I ratio) was calculated.

2.2. Sympathetic skin response (SSR): For the evaluation of sympathetic skin reaction, all children were investigated in a dark and silent room, in a supine position, with their eyes closed. A short rectangular electric stimulus (10 mA, 0.1 ms duration) over the glabella, sympathetic skin reaction was recorded with surface electrodes (palmar and plantar) with a dedicated device (Keypoint, Natus Europe GmbH, München, Germany). The mean latency of 2 responses, one from each side of the body, was calculated in order to screen for sympathic ANS dysfunction.

2.3. Quantitative pupillography: Using a pupillograph (AMTech Pupilknowlogy GmbH, Weinheim, Germany), pupil diameter in darkness (PDD) was detemined. Pupillary light reflex was measured over a period of 2 seconds (intensity of light stimulus: 10^4 cd/m^2, duration of stimulus 200 ms) and several parameters were obtained: relative light reflex amplitude, latency, constriction velocity, early re-dilation velocity (RDV). The mean value of 2 stable measurements of the left eye were used for further analyses 8.

Results: Final analysis included 858 children, 50.6% boys, with a prevalence of obesity ranging between 7.5% and 16.2% according to the International Obesity Task Force and percentage of body fat criteria, respectively. The average dilation velocity was significantly higher among children with obesity, regardless of BMI criteria.

Conclusions: Our results suggest that obesity in children is associated with a dysautonomia in autonomic nervous system, namely with changes in sympathetic activity. Moreover, this findings provide support for the role of the autonomic nervous system in the interaction between lifestyle, diet and the BMI in children.

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