Original article

Early cardiovascular autonomic dysfunction, β cell function and insulin resistance in obese adolescents

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Abstract. *Aims:* The aim of this study was to assess the metabolic and cardiovascular autonomic phenotype in adolescent obesity. *Methods:* Eighteen non diabetic obese individuals and ten lean age-matched control adolescents were included in the study. All subjects underwent Oral Glucose Tolerance Test (OGTT) with insulin and glucose determination for the calculation of AUC, OGIS, QUICKI, and disposition index. Cardiovascular assessments included 24-hour Holter ECG for HRV measurements, ABP monitoring and echocardiography. *Results:* Obese adolescents had higher serum lipids, reduced insulin sensitivity and higher insulin resistance. Obese individuals showed indeed a normal beta-cell function, with insulin AUC and disposition index similar to controls. However, obese adolescents presented a progressive reduction of vagal indexes (RMSSD, HF) and an increase in sympathetic indexes (LF, LF/HF), which correlated with OGIS and beta-cell function parameters. *Conclusion:* Adolescent obesity is characterized by insulin resistance with normal beta-cell function. Metabolic modifications may lead to an early impairment of the autonomic pattern. (www.actabiomedica.it)

Key words: obesity, adolescents, autonomic dysfunction, insulin sensitivity

Introduction

The prevalence of overweight and obesity among children and adolescents is rapidly increasing worldwide, representing a critical health issue in both western and developing countries (1-4). Weight gain in youth is associated with significant morbidity and mortality in later years, especially due to cardiovascular diseases (CVDs). Moreover, obesity is associated with the development of type 2 diabetes mellitus (T2DM) in youth, as well as with insulin-resistance and functional failure of pancreatic beta-cells, even when glucose tolerance remains within the normal range (5).

Although the development of severe and complicated atherosclerosis occurs later in life, early indications of cardiovascular dysfunction, that contribute to the pathogenesis of CVDs, may already begin at a younger age. Autonomic dysregulation has been frequently suggested as a causal link between unhealthy lifestyles, such as overeating, sedentary life-style, and metabolic abnormalities, as evidenced by the metabolic syndrome. Liao et al. have shown that depressed heart rate variability (HRV) in hypertensive diabetic patients is associated with an increased fasting plasma insulin concentration (6). Pikkujamsa et al. have also reported that HRV in hypertensive individuals with insulin resistance syndrome is lower than in subjects without insulin resistance syndrome (7). More recently, Grassi et al. used microneurography to provide evidence that the metabolic syndrome is accompanied by sympathetic activation (8).

In this observational study, we investigated the relationship between insulin sensitivity, beta-cell function and cardiovascular autonomic function in a sample of obese adolescents and in lean age-matched individuals.

Methods

Subjects

Twenty-eight consecutive female adolescents were studied. Eighteen were obese subjects (mean age 12.7±0.2 yrs) with no family history of diabetes, referred for the evaluation and treatment of their overweight (obese). Ten were lean subjects (mean age 12.8±0.4 yrs) with no family history of diabetes, referred for the occasional finding of impaired fasting glucose.

All subjects were healthy Caucasian (Italian ancestry), presented normal thyroid function and were not taking any medication. A detailed medical and family history was obtained from all subjects, and physical examination was performed, including puberty staging. Body weight was measured with a digital scale and height was measured with a wall-mounted stadiometer. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI above the 97th percentile for age and sex, according to TJ Cole normograms (9). Written informed parental consent and adolescent assent were obtained before testing.

Metabolic testing procedures and beta-cell function evaluation

During the observation period, all subjects followed a weight-maintenance diet consisting of at least 250 g of carbohydrates for the 5-7 days before the study. On the first study day, they were evaluated at 8 a.m. after a 12-hour overnight fast. After the local application of a topical anaesthetic cream, an antecubital intravenous catheter was inserted for blood sampling; patency was maintained by slow infusion of normal saline solution. Two baseline samples were then obtained for the measurement of plasma glucose, insulin and lipids. Subsequently, flavoured glucose at a dose of 1.75 g per kilogram of body weight (up to a maximum of 75g) was orally given, and blood samples were obtained at 60, 120 and 180 min.

Areas under the curve (AUC) for glucose and insulin during the 3-hour test time were calculated with the trapezoidal rule. Dynamic (suprabasal) AUC were calculated by subtracting the product of fasting level times from the total AUC during the observation period. Insulin sensitivity was assessed in fasting conditions with the quantitative insulin sensitivity check index (QUICKI) (10) and in dynamic conditions with oral glucose insulin sensitivity (OGIS) (11), which describes glucose clearance during the postprandial phase of the OGTT. Both indices have been extensively validated versus the glucose clamp and are widely used (11, 12). A recent study has shown that QUICKI represents insulin sensitivity mainly on the part of the liver, while OGIS describes insulin action in the peripheral tissues (muscle and fat) (12). Beta-cell function was assessed with the insulinogenic index, defined here as the ratio of dynamic insulin AUC to dynamic glucose AUC. This index quantifies the insulin delivered under glucose stimulation throughout the OGTT. Finally, since beta-cell function cannot be evaluated unless it is related to ambient insulin sensitivity (13), we multiplies OGIS by the insulinogenic index. This product, called the disposition index, was previously used for the intravenous glucose test (13). It estimates the ability of the beta-cell to increase its own response to compensate for increased insulin resistance (13).

Evaluation of cardiac autonomic function

The day after OGTT, blood pressure (BP) was recorded according to the Working Group on High Blood Pressure in Children and Adolescents (14). Physical activity was recorded as weekly hours of sports or playing activity, including school gym classes. Three BP measurements at 5 min interval were taken with the patients sitting after they had rested; the average of the recordings was considered for the study. Thereafter, simultaneous 24-hour ECG Holter and ambulatory BP monitoring (ABPM) was per-

formed. ABPM was obtained using Spacelabs 90207 (Spacelabs Inc. Redmond, Washington, USA). Recording started at about 11 am and was programmed for every 15 minutes over a 24-hour period. BP values were averaged to obtain 24-h, day-time (from 7 am to midnight) and night-time (from midnight to 7 am) BP data. Subjects were requested to remain awake during the daytime and to practice only light physical activity. Moreover, they were requested to have breakfast between 8 and 9 AM, lunch between 12 and 2 PM, and dinner between 7 and 8:30 PM. Snorers or adolescents suffering from apnoea episodes were excluded (information gathered from the parents). At the beginning of the 24-hour monitoring session, the readings of the automatic recorder were compared with those simultaneously measured with a mercury sphygmomanometer; a difference of ±5 mmHg was considered an adequate agreement between the two methods. Measured values of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were stored in a digital memory and downloaded from the monitor to an IBM PC using custom-designed software. If a BP recording had less than 70% successful readings it was rejected and repeated.

The heart period was obtained from the 24-hour ECG Holter tracings; rate was recorded using a tape recorder (Premier Holter 4000, Diagnostic Monitoring, USA), with a phase–locked loop motor speed control to ensure speed stability. The recording speed was 2 mm s-1, the sampling rate was 300 HZ. The Holter ECG software was used to transfer the patient data and to identify and label each QRS complex. Premature ventricular complexes and their adjacent RR intervals were rejected by the software, in addition to electrical noise or other aberrant ECG findings, in according to Berntson's algorithm (15). The night-time period was the same as for ABPM.

Power spectral analysis, performed by Fast Fourier transformation, was obtained every 10 minutes. For each time segment, the power was quantified in total spectral power (TP: the energy in the heart period power spectrum between 0.003 and 1.0 Hz); ultralow frequency + very low frequency (ULF+VLF: the energy of the spectrum below 0.04 Hz). In long term recordings this component accounted for 95% of total power, although their physiological correlates are unknown: they are probably related to physical activity, thermoregulatory and hormonal influences, low frequency spectral power (LF: the energy in the heart period power spectrum between 0.04 and 0.15 Hz), which is an index of both sympathetic and parasympathetic nervous activity; high frequency spectral power (HF: the energy in the heart period power spectrum between 0.15 and 0.4 Hz), which reflects parasympathetic nervous activity. LF and HF were averaged to obtain day and night-time LF and HF levels (16).

Spectral components of HRV were analysed such as absolute units and the LF and HF components such as normalized units (NU= LF or HF/(TP-(VLF+ULF))). The ratio between LF and HF power, an index of cardiac sympathovagal balance, was calculated (17). Normalized power, as well as the LF/HF ratio, provided an assessment of the fractional distribution of power across the frequency axis, and emphasizes the controlled and balanced behaviour of the two branches of the autonomic nervous system irrespective of the total power.

In order to evaluate total and long term HRV, the following time domain (TD) parameters were calculated for the entire recording period: mean normal to normal intervals (NN), and standard deviation of all the cycle intervals (SDNN).

Differences between successive normal RR intervals provided an index of parasympathetic nervous activity. The number of pairs of adjacent RR counts differing by more than 50 ms divided by the total number of all RR intervals (PNN50) was calculated. The RMSSD, a continuous measure of vagal tone, was calculated on the RR intervals by means of the Von Neumann et al. formula (18).

The subjects were also studied with M-mode and two dimensional echocardiography. The examination was performed 48 to 72 hours after ABPM and Holter recording, using an ATL HDI 3500 with a phased array P 3-5 MHz transducer. Echocardiograms were coded and read by an investigator unaware of the clinical data of the children. Left ventricular (LV) internal diameter and wall thickness were measured at end-diastole. Measurements were taken according to the American Society of Echocardiography recommendations (19). Left ventricular mass (LVM)

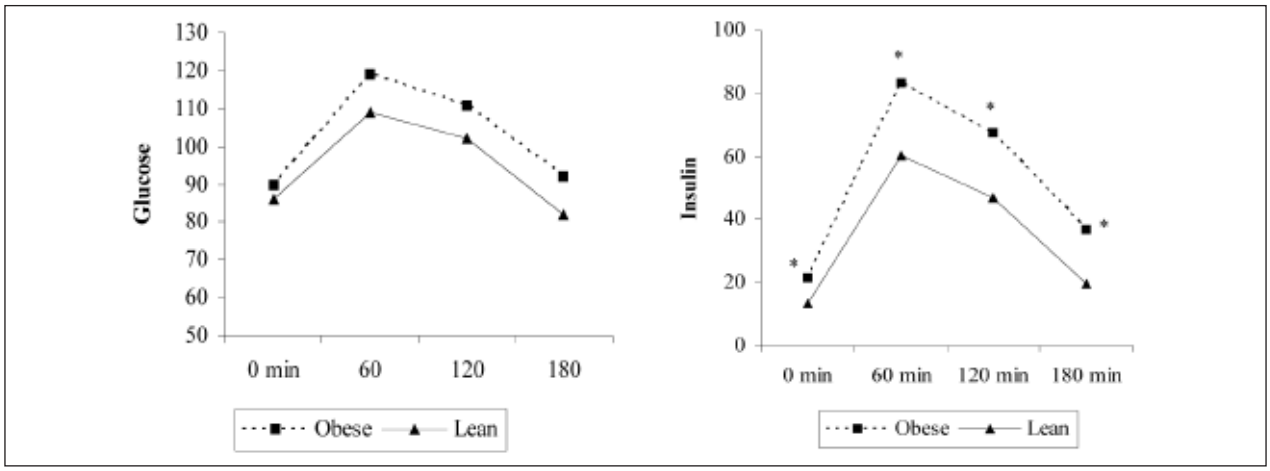

Figure 1. Glucose and insulin pattern during OGTT. * p<0.05 vs lean

was calculated using the formula: LVM = 0.8 x [1.04 x (IVS+LVDD+PWTD)^3) x LVDD^3]+0.6, where IVS is interventricular septum, LVDD left ventricular diastolic dimension and PWTD posterior wall thickness. In order to minimize the effects of body size on left ventricular mass, it was corrected for height^{2,7}. Moreover left ventricular relative wall thickness (RWT) was calculated by the formula: RWT = IVS+ PWTD/LVDD

Statistical analysis

Data and results are expressed as mean±SD. Comparison among the groups was evaluated using one way ANOVA and Bonferroni testing. The differences among spectral HRV parameters were calculated after log transformation of the values (data not shown). The correlation between the parameters of insulin sensitivity and the parameters of HRV was determined using the Spearman rank test. A p value <0.05 was considered as statistically significant.

Results

Clinical data of the two groups of adolescents are reported in Table 1. Obese individuals showed significantly higher triglycerides and lower HDL cholesterol values than lean adolescents. OGTT patterns are shown in Fig. 1 and metabolic parameters are reported in Table 2. During OGTT, insulin levels were significantly higher in obese subjects.

Fasting (QUICKI) and dynamic (OGIS) insulin sensitivity were reduced in obese subjects, but their higher insulin resistance was accompanied by an increased beta-cell response, so that their disposition index remained similar to that of the lean control subjects. No significant differences in office and ABPM blood pressure values were found among the two

Table 1. Basal characteristics of the study population

	Obese	Lean
N	18	10
Age (years)	12.7±0.2	12.8±0.4
BMI	29.8±0.8*	18.8±0.4
Fasting glucose (mg/dl)	90±2	86±1
Fasting insulin (μU/ml)	21.7±2.1*	13.3±0.7
Total cholesterol (mg/dl)	174±8	167±9
High density lipoprotein cholesterol (mg/dl)	44±2*	57±5
Low density lipoprotein cholesterol (mg/dl)	107.2±31.9	98.2±23.3
Triglycerides (mg/dl)	116±12*	63±8

Data are mean ±SD
BMI, body mass index;
* p<0.05 vs lean

Table 2. Beta-cell function and insulin resistance

	Obese	Lean
Total AUC-glucose	192.9±4.7*	176.7±4.8
Total AUC-insulin	10.8±1.05*	7.4±0.67
OGIS	415±11	503±16
QUICKI	0.133±0.008	0.14±0.003
Insulinogenic index total	55.81±4.9*	41.89±3.7
Disposition index	22.68±1.8	21.1±2.05

Data show mean ±SD
AUC, area under the curve; OGIS, oral glucose insulin sensitivity; QUICKI quantitative insulin sensitivity check index
* p<0.05 vs lean

Table 3. Office and 24 h ambulatory blood pressure monitoring

	Obese	Lean
SBP	125±3*	116±3
DBP	78±2	70±3
Office-HR (b/min)	79±9	73±9
SBP 24 hr	115.6±6.7	110.5±7.3
DBP 24 hr	66.6±4.7	64.4±3.7
SBP Day	119.3±7.8	113.5±7.9
DBP Day	70.7±5.6	68.1±5.5
SBP Night	108.1±7.9	103.6±8.9
DBP Night	57.3±6	55.5±3.2

Data show mean ±SD
SBP, systolic blood pressure; DBP, diastolic blood pressure, HR, heart rate
* p<0.05 vs leans

groups (Table 3). Spectral and time domain HRV analysis are reported in Table 4. High frequency normalized unit (HFNU) Time domain parameters of vagal activity (PNN50, RMSSD) were significantly decreased in the obese subjects. LF/HF was also increased in these adolescents, as well as total and long term parameters of HRV.

Table 5 shows the echocardiographic parameters of the two groups. None of the studied subjects had left ventricular hypertrophy, although the obese adolescents showed a significant increase in posterior wall thickness in diastole (PWTD) and LVM.

Both insulin sensitivity indices were directly related to PNN50 (p<0.05), while only the dynamic post-prandial sensitivity (OGIS) was inversely related to LVM (r = 0.042, p<0.03) and relative wall thickness (RWT) (r = 0.035, p<0.05). No significant correlations were found between insulin secretion indexes and HRV parameters.

Table 4. Spectral and time domain HRV parameters of the study group

	Obese	Lean
SDNN	119.56±27.78*	142.75±35.34
SDANN	96.72±29.59	115.25±29.5
PNN50	19.61±9.88*	28±11.38
PNN50 night	28.66±12.9*	39.25±13.87
PNN50 day	15.33±9.22*	23.25±11.49
RMSSD	43.83±12.82*	57±20.25
RMSSD night	53.66±16.47*	71.62±29.6
RMSSD day	37.94±11.63*	49.12±16.38
TP	3873.57±1272.16*	5205.25±1941.25
HFNU	36.28±9.72	39.22±7.57
LFNU	60.68±10.25	57.95±7.92
LF/HF	1.87±0.82	1.56±0.51

Data are mean ±SD
SDNN, standard deviation of the normal-to-normal intervals; SDANN, SD of the averages of RR intervals in all 5-minutes segments; PNN50, proportions of differences of adjacent RR intervals > 50 ms; RMSSD, root mean square successive differences; TP, total power; HFNU, high frequency normalized units; LFNU low frequency normalized units; LF/HF low frequency/high frequency
* p<0.05 vs lean

Table 5. Echocardiographic parameters

	Obese subjects	Lean subjects
IVSTD	7.4±0.7	7.1±1.3
PWTD	7.1±0.5*	5.7±1.3
DD	47.4±2.7	46±3.1
LVM/height$^{2.7}$	32.16±4.82*	25.89±6.96
RWT	0.30±0.3	0.24±0.5

Data show mean ±SD
IVSTD interventricular septum thickness in diastole; PWTD posterior wall thickness in diastole; DD diastolic diameter; LVM left ventricular mass; RWT relative wall thickness
*p<0.05 vs lean

Discussion

Obesity, insulin resistance and impaired beta-cell function have been associated with early cardiovascular dysfunction. In the present work, we have examined the relationship between the metabolic indices of insulin sensitivity and beta-cell function and cardiovascular autonomic regulation, in a group of obese adolescents in comparison with age and sex-matched lean control subjects.

In obese adolescents without T2DM and no family history of diabetes, hyperinsulinemia and reduced

insulin sensitivity were not associated with an impaired disposition index. These results are in accordance with previous findings of our group, where metabolic parameters were evaluated by the intravenous glucose tolerance test (20). Other studies reported impaired beta-cell response during the early phase (30 min) after glucose ingestion, independent of the degree of insulin sensitivity in obese normotolerant adolescents and adults (5, 21-23). Interestingly, Arslanian et al. (24) showed that Caucasian children with a family history of diabetes, evaluated with the clamp technique, had lower insulin sensitivity and glucose disposition indices than those without a family history. Moreover, a large multiracial population study showed that, although the mechanisms of adaptation to obesity-related to insulin resistance was similar across ethnic groups, adolescents of ethnic minorities (expecially African Americans) had a significant impairment of the acute response in the context of severe insulin resistance (25). Hence, an impaired balance between insulin sensitivity and insulin secretion appears to be genetically determined: this may partially explain the higher prevalence of T2DM in young obese people belonging to specific familial or ethnic groups.

In our study group, adolescent obesity was characterized by sympathovagal imbalance comprising a marked reduction in tonic cardiac vagal outflow and an increase in the indices of sympathetic hyperactivity. Interestingly, we showed that parasympathetic parameters were inversely related to the insulin sensitivity indices, i.e. QUICKI and OGIS. On the contrary, they did not correlate with parameters of insulin secretion. The observed autonomic impairment was not confounded by blood pressure, since blood pressure levels were normal in this study population.

Our findings, despite the small number of patients,are in line with previous evidence. Firstly, experimental models and clinical data have shown a clear association between the severity of insulin resistance and the impairment of BRS and signs of vagal activity (26, 27). Also, reduced HRV represents a well-established negative prognostic indicator in hypertension (28) and other cardiovascular conditions (29). Moreover, several lines of evidence suggest that obesity-related hypertension and target organ damage may bear a significant neurogenic component. Finally, therapies aimed at reducing weight, particularly caloric restriction and aerobic exercise, commonly reduce autonomic dysfunction and insulin resistance (30).

Sympatho-vagal imbalance may have several deleterious cardiovascular effects, including the stimulation of cardiac and vascular remodelling by induction of cardiomiocyte and vascular smooth muscle cell growth (31, 32), increased myocardial oxygen consumption and peripheral vascular resistance (33). In patients with the metabolic syndrome, the relative left ventricular wall thickness and the prevalence of altered left ventricular patterns (LVH and left ventricular concentric remodelling), defined according to prognostically validated sex-specific echocardiographic criteria indexed to body surface area, are significantly higher than in patients not presenting the syndrome (34). Accordingly, in the present study, adolescent obesity was associated with a significantly increased left ventricular mass and a trend toward concentric remodelling in comparison with lean subjects.

In conclusion, childhood and adolescent obesity is of special significance because of its increasing prevalence and its association with insulin-resistance, sympathetic overactivity and other cardiovascular risk factors. The evaluation of the autonomic pattern may be an additional and useful tool to monitor the early cardiovascular impact of overweight and efficacy of therapeutic and lifestyle interventions.

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