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Vascular health in severely obese adolescents: effects of weight loss

Submission date
11/03/2013

Recruitment status
No longer recruiting

Registration date
16/04/2013

Overall study status
Completed

Last Edited
06/04/2021

Condition category
Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Obese children are at a higher risk than thought of developing vascular diseases. Besides the harmful effects of obesity, children's vascular health may worsen as they pass through puberty into adulthood, accelerating the process of atherosclerosis. One of the fastest growing obesity categories in children is severe obesity, showing a 300% increase in the US since 1976. We will evaluate vascular health in 20 severely obese adolescents, before and after 4 months of diet and exercise, which are essentials components of lifestyle programs. We also will assess vascular health in 20 normal-weight adolescents to serve as controls. We previously found that pre-pubertal obese children had impaired vascular capability to dilate, which is a primary function of all blood vessels. Therefore, the specific aim of this project is to analyze the effects of weight loss on the vascular capability to dilate in severely obese adolescents. The main question to be answered is whether weight loss could improve vascular function in this population. According to very encouraging outcomes found in severely obese adults we expect to get positive results with weight loss. If vascular function were not improved, a new focus of attention for vascular risk in childhood obesity would be pointed out: the adolescence period. This might also be a step forward towards an optimal strategy to preserve vascular health in this vulnerable population and to escape the vicious circle of atherosclerosis.

Who can participate?
This study aims to recruit about 25 severely obese adolescents and 25 normal- weight controls (pubertal stage ≥ 2 years) from a pediatric weight centre located in Sanary-sur-mer (France) and the local community.

What does the study involve?
We will evaluate vascular health in 25 severely obese adolescents, before and after 4 months of diet and exercise. We also will assess vascular health in 25 normal-weight adolescents who will serve as controls.

What are the possible benefits and risks of participating?
There will be no immediate direct benefit to those taking part. But there should be benefits to future severely obese adolescents and to the country's health care system because the results of the study are likely to improve how this vulnerable population is considered and treated.

A potential risk could be for severely obese and normal-weight adolescents with contraindications to exercise. All adolescents will have a complete medical check-up before starting the intervention. We will only recruit adolescents with no contraindications to exercise. Some methods of evaluation may be unfamiliar to the adolescents. This study is based on non-invasive techniques of vascular evaluation. The only invasive technique we use is the blood collection procedure. However, if the adolescent is reluctant, they will not have a blood test.

Where is the study run from?
This study was run by the University of Avignon and the Nimes University Hospital (France).

When is study starting and how long is it expected to run for?
The study ran between June 2011 and March 2012.

Who is funding the study?
Funding has been provided by the French Society of Vascular Medicine (France).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
SFMV2010

Study information

Scientific Title

Macro- and microcirculation in severely obese adolescents: effects of a 4-month weight loss program

Acronym
CODE (Circulation - Obese - Diet - Exercise)

Study objectives
The prevalence of severe obesity in the US pediatric population have tripled in the last three decades, becoming one of the fastest growing categories of childhood obesity (Skelton et al., 2009), which is associated with vascular risk factors and disease in adulthood (Must et al., 1992). Moreover, the progressive exacerbation of preclinical signs of vascular disease might be particularly accelerated in obese adolescents on account of the pro-inflammatory and pro-oxidative changes, plausibly hampering vascular function, occurring during puberty (Montero et al., 2012). A particular emphasis is thus placed on the detection of vascular alterations in childhood obesity before irreversible consequences manifest. Perturbation of conduit artery function is one of the earliest manifestations of atherosclerosis and is considered a seminal event in its initiation (Raitakari and Celermajer, 2000). Impaired vasodilation of the brachial conduit artery was previously reported in severe obese children and adolescents (SOA) (Tounian et al., 2001). The microcirculation, in turn, is increasingly recognized to be independently involved in vascular diseases previously thought to be essentially a question of the macrocirculation (Wiernsperger and Rapin, 2012). Yet, to date, there is poor comprehension of the microvascular function state in severe childhood obesity (Schlager et al., 2011). Furthermore, the specific vascular profile of severely obese adolescents (SOA) in unknown, since the aforementioned studies included pre-pubertal children (Schlager et al., 2011; Tounian et al., 2001). Lifestyle interventions consisting of physical activity and/or diet have been successful in improving vascular function and altered markers of inflammation and oxidative stress in moderate obese children and adolescents (Montero et al., 2012). However, no related information is available on severe childhood obesity.

Therefore, the aims of the present study were:
1. To investigate, in a comprehensive way, the vascular function in the macro- and microcirculation of severely obese and normal weight adolescents
2. To determine the longitudinal effects of a weight loss program on both vascular beds in SOA

Ethics approval required
Old ethics approval format

Ethics approval(s)
Comite de Protection des Personnes Sud de la Mediterranee III. Date of approval; 19/01/2011. Reference numbers: 2010-A01328-31 (AFSSAPS: Agence Française de Sécurité Sanitaire des Produits de Santé, 25/02/2011).

Study design
1. Case-control study comparing severely obese adolescents (SOA) and normal-weight controls
2. Longitudinal study before and after a weight loss program in a pediatric weight center

Primary study design
Observational

Secondary study design

Case-control study

Study setting(s)
GP practice

Study type(s)
Quality of life

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Severe obesity in adolescents

Interventions
Since their admission in the pediatric weight center, the SOA group will undergo a 4-month weight loss program consisting of diet and exercise. SOA will receive a moderately hypocaloric diet (reduction of ~500 calories/day) based on a balanced distribution of carbohydrates (55%), proteins (15%), and lipids (30% total, with less than 10% saturated fat), while performing a physical activity program consisting of four 90-minute supervised sessions per week for 4-months. Each session will involve aerobic exercise, including dancing, tennis, and recreational games, intended to encourage physical activity in the subjects.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
1. Endothelium-dependent and independent dilation in the brachial conduit artery: Macrovascular assessment of the brachial conduit artery will be performed according to the International Brachial Reactivity Task Force Guidelines (Corretti et al., 2002). Brachial measurements will be achieved using high-resolution vascular ultrasonography (MyLab30, Esaote SpA, Firenze, Italy), with a 10-MHz multi-frequency linear probe. The ultrasound probe will be placed approximately midway between the antecubital and axillary regions. To assess endothelium-dependent vasodilation, the brachial artery diameter will be measured before, during and after reactive hyperemia (flow-mediated dilation, FMD). Reactive hyperemia will be induced by inflating a pneumatic cuff on the right forearm near the elbow to 250 mm Hg for 5 minutes and then deflating it. Fifteen minutes later, baseline measurements will be repeated, before and after sublingual administration of 0.4 mg of isosorbide dinitrate (Isocard, Schwarz Pharma, Monheim, Germany), an organic nitrate considered to be an endothelium-independent vasodilator (nitrate-mediated dilation, NMD) assessing arterial smooth muscle function. This procedure is described in detail elsewhere (Karpoff et al., 2009). B-mode images, Doppler signals and electrocardiographic data will be recorded and stored for offline analysis. FMD and NMD will be expressed as the percentage change of peak diastolic brachial diameter after reactive hyperemia and organic nitrate administration, respectively, relative to the baseline diastolic diameter. Time-averaged mean blood flow velocity and blood flow will be determined, as previously described (Walther et al., 2006). Shear rate (s-1) will be calculated as 4 × time-averaged mean blood flow velocity/mean brachial diameter, to estimate resting and peak shear

stress (Betik et al., 2004). Normalization of FMD by the net shear rate stimulus (peak minus resting shear rate, Δshear rate) will be explored to take into account the impact of shear rate on FMD. Within-subject coefficient of variations in our laboratory at rest are 1.8% for arterial diameters, 13.2% for time averaged mean velocity and 12.7% for blood flow (Walther et al., 2006).

2. Endothelium-dependent and independent perfusion in the cutaneous microcirculation: Microvascular assessment of cutaneous blood flow (CBF) will be performed by means of the laser Doppler flowmetry (LDF) technique. LDF continuously monitors perfusion by measuring microvascular red blood flow using the Doppler principle. The technique of LDF has been described in detail elsewhere (Leahy et al., 1999). Cutaneous blood flow (CBF) will be measured in conventional perfusion units (PU) using a LDF system (Periflux PF 5000, Perimed, Stockholm, Sweden), equipped with a thermostatic LDF probe with an effective surface of 0.95 cm2 (PF 481, Perimed, Stockholm, Sweden), on the volar surface of the left forearm. Before the beginning of the iontophoresis protocol, resting forearm CBF will be calculated by averaging a 3-minute steady recording using a non-drug-containing LDF probe. A direct current for drug iontophoresis will be provided by a battery-powered current stimulator (Perilont, Perimed, Stockholm, Sweden). Iontophoresis allows non-invasive drug delivery to the skin without systemic effects and perturbation of the skin (Morris et al., 1995). Microvascular responses to iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP) will be assessed. SNP 1% and ACh 1% solutions, adjusted to a physiological ionic strength (0.154 M) by addition of saline, will be delivered via two drug delivery electrodes, each inserted within an LDF probe, positioned 10 cm apart avoiding superficial veins and broken epidermal areas. In order to minimize non-specific vasodilatory effects, the iontophoresis protocol will consist in a single anodal (ACh) or cathodal (SNP) pulse of 0.021 mA/cm2 for 370 s, yielding a total charge of 7.8 mC/cm2 (Droog et al., 2004; Durand et al., 2002). In addition, a non-drug containing LDF probe will determine the CBF response to sublingual administration of organic nitrate (NMD). LDF probes will be maintained at a constant temperature of 33°C all along the above measurements. To assess the local hyperthermia response, a non-drug containing LDF probe will be heated to 42°C for 5 minutes.

References

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Droog, E. J., et al., 2004. A protocol for iontophoresis of acetylcholine and sodium nitroprusside that minimises nonspecific vasodilatory effects. Microvasc Res. 67, 197-202.
Durand, S., et al., 2002. Vasodilatation in response to repeated anodal current application in the human skin relies on aspirin-sensitive mechanisms. J Physiol. 540, 261-9.
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Leahy, M. J., et al., 1999. Principles and practice of the laser-Doppler perfusion technique. Technol Health Care. 7, 143-62.
Morris, S. J., et al., 1995. Responses of the skin microcirculation to acetylcholine and sodium nitroprusside in patients with NIDDM. Diabetologia. 38, 1337-44.
Walther, G., et al., 2006. Femoral and axillary ultrasound blood flow during exercise: a methodological study. Med Sci Sports Exerc. 38, 1353-61.

Secondary outcome measures

Blood analysis:

Fasting blood samples will be collected after an overnight fast. Biochemical markers related to vascular function such as leptin, resistin, C-reactive protein, myeloperoxidase, and tissue plasminogen activator will be determined in plasma by bead-based multiplex immunoassays (FlowCytomix, eBioscience, San Diego, CA, USA). Plasma insulin will be measured using the radioimmunoassay method (coat-a-count radioimmunoassay kit TKIN2, Siemens, Berlin, Germany).

Overall study start date
01/06/2011

Completion date
01/03/2012

Eligibility

Key inclusion criteria
1. Adolescents with severe obesity. BMI z-scores greater than 3 defined severe obesity
2. Healthy normal-weight matched for gender and pubertal stage to serve as controls
3. All subjects will be normotensive (defined as a pressure < 95th sex-, age-, and height-specific percentiles), non-diabetic, and free from further known obesity-related comorbidities

Participant type(s)
Patient

Age group
Child

Sex
Both

Target number of participants
50

Total final enrolment
49

Key exclusion criteria
1. A family history of premature cardiovascular disease
2. Intake of any medication
3. Pubertal status assessed by Tanner stage < 2
4. Weight loss larger than 5% of their total weight during the previous 3 months
5. Non-sedentary status (> 3 h of exercise per week) to minimize training effects

Date of first enrolment
01/06/2011

Date of final enrolment
01/03/2012

Locations

Countries of recruitment
France

Study participating centre
Service dExploration et Médecine Vasculaire Pr Dauzat
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Sponsor information

Organisation
French Society of Vascular Medicine Research (Société Française de Médecine Vasculaire) (SFMV) (France)

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Sponsor type
Research organisation

Website
http://www.portailvasculaire.fr/espace-sfmv/sfmv

ROR
https://ror.org/01jatd098

Funder(s)

Funder type
Research organisation

Funder Name
French Society of Vascular Medicine Research (France) Grant 2010-2012.

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/03/2014		Yes	No
Results article	lipoprotein results	06/05/2021	06/04/2021	Yes	No