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CAN WE IMPROVE THE EVALUATION OF CARDIOVASCULAR RISK IN OBESE CHILDREN? A POSSIBLE STUDY PROTOCOL

MIHAI OCTAVIAN NEGREA[1], MIHAI LEONIDA NEAMȚU[2]

[1] *"Niculae Stăncioiu" Emergency Heart Institute for Cardiovascular Diseases, Cluj-Napoca,* [2] *"Lucian Blaga" University of Sibiu*

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Abstract: *The link between obesity and a wide range of cardiovascular disorders is well known.(1,2) In recent years, the prevalence of obesity has reached an alarming level.(3) Unfortunately, the situation is similar for the paediatric population – which may provide a perspective on the continuously growing global burden of this affliction.(4) Acting upon this issue is a fundamental direction in modern preventive medicine. A firm action starting in childhood may prove itself to be more beneficial the sooner it is implemented. Multiple anthropometric, clinical, laboratory and imaging parameters have been related to the presence of obesity and cardiovascular risk. This article represents a proposal for a possible protocol of a study aimed at paediatric obesity as a cardiovascular risk factor and aims to construct a model for a therapeutic intervention in these patients.*

INTRODUCTION

The link between obesity and a wide range of cardiovascular disorders is well known.(1,2) In recent years, the prevalence of obesity has reached an alarming level.(3) Unfortunately, the situation is similar for the paediatric population – which may provide a perspective on the continuously growing global burden of this affliction.(4) Acting upon this issue is a fundamental direction in modern preventive medicine. A firm action starting in childhood may prove itself to be more beneficial the sooner it is implemented. Thus, it would be possible to reduce the product between the severity of obesity and the exposure time of this risk factor, with a more pronounced preventive potential when both of these parameters are targeted.(5)

Multiple anthropometric, clinical, laboratory and imaging parameters have been related to the presence of obesity. These factors are commonly found in correlation with the cardiovascular risk of patients, whether they are paediatric or adult. When considering the concept of cumulative exposure (the product between the severity of a risk factor and the time of exposure), the necessity of an intervention in the subclinical phase of cardiovascular impairment becomes apparent.

This article represents proposal for a possible protocol of a study aimed at paediatric obesity as a cardiovascular risk factor and aims to construct a model for a therapeutic intervention in these patients. Many efforts have been made regarding the quantification of cardiovascular risk and in order to obtain a more suitable description for obese patients. The parameters developed in this regard are briefly summarized in the following section. They have been divided according to the method in which the corresponding data has been collected.

Risk factors obtained from medical history. As in any pathology, a detailed history can be useful in highlighting factors that lead to the development of cardiovascular pathology or obesity, therefore the risk factors that can be obtained in this manner are, in fact, the first ones that are obtained when coming into contact with a patient. A relevant example is significant family history, such as first-degree relatives with obesity or cardiovascular disease that correlate with atherogenesis (such as hypertension, ischemic heart disease, peripheral artery disease, stroke, aortic atheromatosis) or diabetes mellitus. Early onset of these afflictions within first-degree relatives (i.e. onset under 50 years of age) provides the most relevance. Furthermore, by means of obtaining a detailed medical history, data related to eating habits, the sleep-wake cycle, sedentary lifestyle or regular physical activity and non-academic screen time can be documented. This information provides an approximate view on the genetic load of an individual, as well as data related to environmental exposures. All of these factors can provide information about the risk of developing cardiovascular pathologies. In addition, the aforementioned process can highlight potential targets for reducing cardiovascular risk by identifying modifiable risk factors.(6)

Anthropometric measurements. There are a number of anthropometric parameters that can be used to define obesity, which correlate with cardiovascular risk. Body mass index (defined as the ratio between the weight of an individual in kilograms and the square of his or her height) is a parameter that is commonly used for defining the overweight or obese status in clinical practice.(7) However, there are a number of other parameters that have proved to be more useful in certain regards. Abdominal circumference, for example is a parameter used in defining the metabolic syndrome and has shown in certain studies a more significant relationship to the presence of high blood pressure. Further examples of parameters that correlate with cardiovascular risk are the waist-hip ratio and waist-height ratio.(8) There are also a number of relatively new parameters which have been used in recent studies, such as the ABSI (a

[2]Corresponding author: Mihai Leonida Neamtu, Str. Tipografilor, Nr. 25, Apt. 3, Sibiu, România, E-mail: mihai.neamtu@ulbsibiu.ro, Phone: +40770 186073

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body shape index - calculated using the abdominal circumference, BMI and height) and the hip index (a variant of the hip circumference which is indexed to the normal value of this parameter).(9) The circumference of the neck has shown to be related to a number of respiratory pathologies (10), which, in turn are often associated with cardiovascular disease.(11)

Clinical findings. From a clinical standpoint, determining the heart rate and blood pressure can bring forth the hyper-dynamic status of obese paediatric patients.(12) This can be observed even in the preclinical stage, when despite the fact that the measured values are still within the reference ranges, they are on average higher than non-obese patients of the same age.(13)

Laboratory findings. There are a number of laboratory tests with known relevance for the development of cardiovascular pathologies. The atherogenic lipid profile, identifiable by the measurement of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceridemia, is widely used in everyday clinical practice to predict the cardiovascular risk of examined patients.(14-16) However, one parameter that has not yet been implemented in wide-spread use is the atherogenic plasma index (defined as the logarithm of the ratio of seric triglycerides and HDL-cholesterol). This parameter appears to have a closer correlation with cardiovascular risk when compared to the value of each of its' individual components.(17,18) The measurement of fasting blood glucose and glycated haemoglobin are used for the diagnosis of diabetes, but they are also useful in defining prediabetes or altered basal glycaemia - entities that predict the development of this pathology with important and well-known cardiovascular resonance.(19,20) Another parameter that can provide information on preclinical diabetes mellitus, especially in obese patients, is the insulin resistance index (HOMA-IR - Homeostatic Model Assessment for Insulin resistance), defined as the product of blood glucose and circulating insulin taken under baseline conditions.(13,21) Circulating uric acid has also been shown in some studies to have a role in defining the preclinical stage of cardiovascular disease, a role that has to date been underestimated.(22) Proinflammatory status also plays an important role in the development of cardiovascular pathologies. The value of C-reactive protein is commonly used to provide information on inflammatory status, which correlates with the presence of cardiovascular disease.(23,24) This measurement (especially in its' high-sensitivity variant - hsCRP), however, has certain cost-related limitations in clinical screening.(25) For this reason, there have been attempts to define more accessible parameters to quantify chronic inflammation.

A relevant example is the neutrophil-lymphocyte ratio. This ratio correlates with a wide range of cardiovascular diseases, as well as with the results of therapeutic interventions, especially regarding coronary heart disease. A possible explanation lies in the fact that neutrophils play an important role in the nonspecific inflammatory response, and their increase (even before exceeding the thresholds of normal values) mirrors the increase in oxidative stress in the body, while the decrease in lymphocyte numbers correlates with a general precariousness of the immune system.(26-30) Other factors related to the proinflammatory (and implicitly prothrombotic) status are the platelet-lymphocyte ratio and the platelet distribution width.(31) In addition to these measurements, there is a particular current interest in dosing circulating microRNA. These are short nucleotide sequences that do not encode proteins, but are involved in the expression of certain genes.

Despite the ubiquitous presence of nucleases in the bloodstream, a number of microRNA molecules appear to maintain their stability and exhibit significant circulating values. The way they perform their function related to mRNA translation. By destabilizing the target mRNA, circulating microRNAs inhibit their translation and hinder the synthesis of certain proteins. The exact details regarding the source of synthesis and secretion of these molecules are not known. Their exact target regions also remain convoluted. Given fact that microRNA sequences are, however, relatively short (20-24 nucleotides) it is possible that each individual microRNA sequence may act upon the expression of several genes. Given these findings, it is hypothesised that circulating microRNAs are part of a complex epigenetic regulating homeostatic system. A study published in the BMC Genes and Nutrition described the possibility of a certain circulating microRNA profile that correlates with the presence of obesity in children.(32)

Imaging findings. Finally, in addition to the risk factors identified through medical history, clinical examination and laboratory measurements, there are also several parameters of interest that can be determined by imaging investigations. Ultrasonographic techniques have become during the last decades some of the most accessible resources in clinical practice. The parameters determined by carotid ultrasound (intima media thickness) and carotid Doppler examination (arterial stiffness indices) have repeatedly shown their connection with the atherogenic process.(33-35) Similarly, Doppler ultrasonography of the renal arteries may provide a useful parameter (Doppler-derived renal resistive index) that is related to renal impairment in this systemic process and is frequently linked to the etiopathogenesis of high blood pressure.(36) Cardiac ultrasound also plays a crucial role in the diagnosis of cardiovascular diseases in everyday practice, and the most modern innovations such as tissue Doppler and speckle-tracking technology have extended its scope beyond the usual techniques employed, with the development of increasingly promising advances in the direction of risk stratification, even in the subclinical phase of cardiac impairment.(37,38) Another imaging method used in cardiac investigation is cardiac MRI. Although it provides a much narrower field of applicability than ultra sonographic methods (particularly due to a more reduced accessibility) it has excellent diagnostic performance in certain cases where other imaging methods are insufficient. One advantage that cardiac MRI provides is the elimination of operator dependence, a known drawback of heart ultrasound. In addition, a substantial advantage over other methods of sectional imaging, especially in the paediatric population, is the absence of radiation exposure.(39) Finally, another interesting use of magnetic resonance imaging, currently confined however to the field of scientific research, is the quantification of visceral fat - a defining factor for metabolic syndrome and predictive for cardiovascular pathology related to atherogenesis.(40)

AIM

In addition to defining a risk profile as described above, the proposed protocol also aims to provide a model for a therapeutic intervention aimed at the reduction of body mass and the analysis that follows such a program. This type of study could provide valuable information regarding the actual dependence of cardiovascular risk on weight status and the quantification of the potential benefit of weight loss as a preventive action.

There is a tendency in the literature to analyse a small group of variables and to consider the parameters described so far as factors with increased individual validity. This has led to a need for a holistic approach to cardiovascular risk factors. One potential approach in this regard is the attempt to implement computer algorithms that can lead to the detection of new composite parameters, with increased predictability for cardiovascular impairment compared to those known so far.

As such, the research niche proposed by this approach refers to the attempt of an integrated approach to the parameters described in the previous paragraphs. Another problem that the current research project is trying to address is the correlation of high-performance investigations (MRI techniques for determining fat mass distribution for example) with more accessible parameters that can be used in regular practice (neutrophil-lymphocytic index, anthropometric parameters, etc.), in order to validate these simpler techniques for use in routine medical activity.

These findings could have an important practical significance, allowing the use of accessible but reliable markers. Last but not least, this project aims to find parameters that correlate with the success of the therapeutic intervention on lifestyle. The predictability of such an event could influence the decision algorithm regarding which therapy should be employed for each patient.

From a logistical standpoint, regarding the methods used for data analysis, in order to achieve the stated objective it would be ideal to use large data sets in order to more efficiently employ artificial intelligence algorithms when searching for correlations.(41-43)

MATERIALS AND METHODS

In order to achieve the proposed objectives, the research project is structured in two stages. The first step consists of selecting a group of overweight or obese paediatric patients, defined according to WHO criteria as having a BMI greater than one or two standard deviations for age-appropriate values (44), and a control group of non-obese paediatric patients.

With regards to age as an inclusion criterion - a wider range would present the advantage of a more accessible population, with the potential risk however of inhomogeneous groups. On the other hand, too narrow a range could yield results that are too particular to draw conclusions of general interest. A compromise variant in this regard is the age range between 8 and 18 years. The control group should be selected in such a manner that there are no significant differences between the study groups regarding demographic variables (distribution by sex, age average and its distribution, distribution by pubertal stages). For these two groups, a series of measurements of the parameters described in the previous section should be made. In this stage of the study the purpose is to emphasize the difference between the study group and the control group, and an attempt will be made to establish the relationship between subclinical cardiovascular impairment and the parameters described as risk factors. Another objective to pursue is the comparison between high performance investigation methods and other, more accessible methods.

The second stage of the project is the therapeutic intervention. A cost-effective and feasible option for long-term follow-up is a specialized nutrition consultation. A lifestyle intervention plan for weight reduction should be established. The key elements of this plan will focus on reducing the caloric intake and optimizing it in terms of the proportions of the dietary principles and eating schedule, in addition to a physical activity plan adapted to each patient.

When considering the duration of the intervention, a feasible option, used in other studies in the literature, is one year.(45) At the end of the intervention period, all the parameters that were studied in the initial stage of the research project should be reassessed. This time, the focus will be on establishing the effect of the intervention on cardiovascular impairment and the risk factors studied. Simultaneously, establishing predictive factors for the therapeutic success of the implemented program should be pursued. In order to reach the latter objective, patients who have had a significant weight loss (over 0.5 of a standard deviation from the initial weight, similar to the method used in (45) will be compared with those who have failed this goal, while taking into account the values determined prior to the beginning of the lifestyle change plan.

When defining the exclusion criteria, considering the fact that the purpose of the study is to reveal the causal relationship between obesity and cardiovascular risk, smokers should be excluded from the study, whose risk may be greatly influenced by the presence of this condition.

Furthermore, due to the aim of the study of defining preclinical impairment, patients with known conditions (cardiovascular, renal, hepatic, endocrinological, chronic or acute inflammatory at the time of presentation) and those following treatments with medications that may affect the distribution of body fat (antipsychotics, antiepileptics, sedatives, antidepressants, anxiolytics, thymostabilizers, antimigraine agents, oral antidiabetics, insulin, glucocorticoids, thyroid hormones, oral contraceptives, diuretics) should be excluded so as not to interfere with the results obtained.(45-47)

Regarding the use of artificial intelligence algorithms, a first step is to define a target variable. For example, in the cross-sectional study to be carried out in the first stage of the research project, subclinical cardiovascular impairment can be quantified as a composite variable consisting of parameters denoting this impairment (table no. 1). For each variable, the presence of organ damage will be defined according to either the normal values known for the respective variable (for example, intimate-media thickness > 0.9 mm (3)), or the presence of a significant difference in the value of an individual versus the control group (determined by statistical tests, such as the one sample-t test for continuous quantitative variables with normal distribution).

Table no. 1. Subclinical cardiovascular impairment – suggested defining independent variables

Data source	Variable (measurement unit)	Variable type	Interpretation
Clinical examination	Heart rate (bpm)	Discrete quantitative	Hyperdinamic circulatory status
	Systolic blood pressure (mmHg)	Discrete quantitative	
	Diastolic blood pressure (mmHg)	Discrete quantitative	
Carotid echography (2D and Doppler)	Intima-media thickness (*ratio*)	Continuous quantitative	Subclinical vascular changes
	Stiffness index β (*ratio*)	Continuous quantitative	
	Arterial compliance (mm^2/kPa)	Continuous quantitative	
	One-point pulse-wave velocity (m/s)	Continuous quantitative	
	Augmentation index (%)	Continuous quantitative	
	Pressure-strain elasticity modulus (kPa)	Continuous quantitative	
Renal artery Doppler examination	Doppler-derived renal resistive index (*ratio*)	Continuous quantitative	Subclinical vascular changes
Cardiac ultrasound (morphological parameters)	Left ventricle systolic volume (ml)	Continuous quantitative	Ventricular hypertrophy
	Left ventricle diastolic volume (ml)	Continuous quantitative	
	Interventricular septum thickness (mm)	Continuous quantitative	
	Posterior wall thickness (mm)	Continuous quantitative	
Cardiac ultrasound (functional parameters)	Left ventricle ejection fraction (%)	Continuous quantitative	Cardiac function impairment
	TAPSE (mm)	Continuous quantitative	
	E/A (*ratio*)	Continuous quantitative	
Cardiac ultrasound (tissue Doppler imaging)	septal s' (cm/s)	Continuous quantitative	
	lateral s' (cm/s)	Continuous quantitative	
	septal e' (cm/s)	Continuous quantitative	
	lateral e' (cm/s)	Continuous quantitative	

Data source	Variable (measurement unit)	Variable type	Interpretation
	septal a' (cm/s)	Continuous quantitative	
	Lateral a' (cm/s)	Continuous quantitative	
	E/e' (*ratio*)	Continuous quantitative	
	e'/a' (*ratio*)	Continuous quantitative	
Cardiac ultrasound (strain imaging)	Global longitudinal strain (%)	Continuous quantitative	
Cardiac MRI (morphological parameters)	Left ventricle systolic volume (ml)	Continuous quantitative	Ventricular hypertrophy
	Left ventricle diastolic volume (ml)	Continuous quantitative	
	Left ventricle wall thickness (mm)	Continuous quantitative	
	Left ventricle mass (body surface area indexed– g/m^2)	Continuous quantitative	
Cardiac MRI (functional parameters)	Left ventricle ejection fraction (%)	Continuous quantitative	Cardiac function impairment

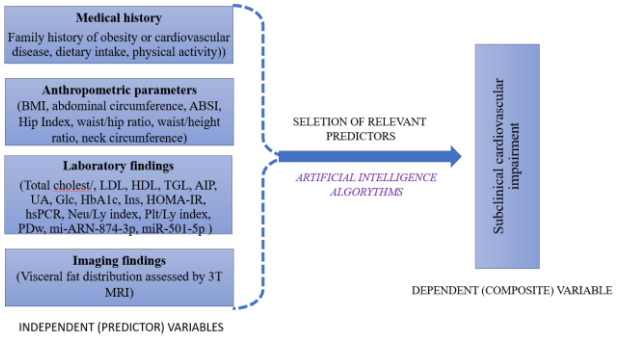
Subsequently, a series of dependent variables are defined. In this case, we propose the variables specified in the following table (table no. 2).

Table no. 2. Suggested dependent variables

Data source	Variable (measurement unit)	Variable type	Interpretation
Anamnestic	Family history of obesity (*YES/NO*)	Qualitative, dichotom.	Establishing genetic predispositions and environmental conditions
	Family history of cardiovascular disease (*YES/NO*)	Qualitative, dichotom.	
	Estimated number of hours spent exerting moderate-to-intense physical activity (*numerical value*)	Discrete quantitative	
	Estimated number of hours of non-academic screen time (*numerical value*)	Discrete quantitative	
	Ratio between estimated calorie intake and optimal calorie intake (*ratio*)	Discrete quantitative	
Anthropom. parameters	Body mass index (kg/m^2)	Continuous quantitative	Establishing body constitution
	Abdominal circumference (cm)	Continuous quantitative	
	ABSI index Z score (*ratio*)	Continuous quantitative	
	Hip Index Z score (*ratio*)	Continuous quantitative	
	Waist-hip ratio *(ratio)*	Continuous quantitative	
	Waist-height ratio (*ratio*)	Continuous quantitative	
	Neck circumference (cm)	Continuous quantitative	
Laboratory findings	Total cholesterol (mg/dl)	Continuous quantitative	Establishment of atherogenic lipid profile, glycaemic balance, proinflammatory status and epigenetic profile
	LDL-cholesterol (mg/dl)	Continuous quantitative	
	HDL- cholesterol (mg/dl)	Continuous quantitative	
	Triglyceride (mg/dl)	Continuous quantitative	
	Atherogenic index of plasma (*ratio*)	Continuous quantitative	
	Uric acid (mg/dl)	Continuous quantitative	
	Fasting seric glucose (mg/dl)	Continuous quantitative	
	Glycated haemoglobin (g/dl)	Continuous quantitative	
	Circulating insulin (µU/mL)	Continuous quantitative	
	HOMA-IR (*numerical value*)	Continuous quantitative	
	High sensitive C-Reactive Protein (mg/L)	Continuous quantitative	
	Neutrophil/lymphocyte ratio (*ratio*)	Continuous quantitative	
	Platelet/lymphocyte ratio (*ratio*)	Continuous quantitative	
	Platelet distribution width (*numerical value*)	Continuous quantitative	
	miR-874-3p circulating micro-RNA (*cycle threshold value – numerical value*)	Discrete quantitative	
	miR-501-5p circulating micro-RNA (*cycle threshold value – numerical value*)	Discrete quantitative	
3T MRI	Visceral fat area (cm^2)	Continuous quantitative	Establishing adipose tissue distribution
	Subcutaneous fat area (cm^2)	Continuous quantitative	
	Visceral/subcutaneous fat area ratio (*ratio*)	Continuous quantitative	

Finally, these data will be introduced in a computer system, and based on the methods described in the literature used for "artificial learning" (41-43) the goal is to establish the optimal algorithm for predicting the probability of subclinical cardiovascular impairment according to the values of the dependent variables defined (figure no. 1).

Figure no. 1. Proposed algorithm



In subsequent studies, the target variables will be defined according to the expected outcome: the success of the therapeutic intervention (weight loss by more than 0.5 standard deviations of weight), or the significant reduction of cardiovascular risk (composite parameter based on significant differences of variables that define subclinical cardiovascular impairment, before and after therapeutic intervention). The dependent variables will in turn be redefined accordingly. For calculating the required size of the sample, given that the target population is infinite, Cochran's formula can be used: $N = Z^2pq/e^2$, where N is the required sample size, e is the desired level of precision (5%), Z is selected critical value of desired confidence level (1.96 for the set value of e = 0.05), p the proportion of patients who achieve a significant decrease in weight (43% in (45)), and q is the proportion of patients who fail to achieve a significant decrease in weight (1-p). According to these calculations, a number of 377 patients is needed to have a representative sample.

ANTICIPATED RESULTS AND DISCUSSIONS

The potential results of the study concern a pressing issue, namely that of the prevention of cardiovascular diseases, in the context of a continuously growing global burden of these pathologies. The accurate establishment of cardiovascular risk, the validation of some techniques in this regard and the attempt to prevent the increase of cardiovascular pathologies through positive action are all important directions in today's practice. Regarding the socio-economic and cultural relevance of the project, the study can provide useful information about the status of the Romanian population, ideally offering a prospect for the implementation of educational strategies and the development of clinical protocols in dealing with the problem of child obesity.

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