ejpmr, 2020,7(5), 179-185

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FUNCTIONAL AND LABORATORY MARKERS IN STRATIFICATION OF THE RISK OF DEVELOPMENT OF CARDIOVASCULAR DISORDERS IN TEENAGERS WITH EXOGENOUS CONSTITUTIONAL OBESITY I DEGREE

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Article Received on 10/03/2020 **Article Revised on 31/03/2020** **Article Accepted on 21/04/2020**

ABSTRACT

The results of studying the thickness of epicardial fat according to echocardiography, as well as a comparative analysis of plasma levels of adiponectin and highly sensitive C-reactive protein (CRPhs), as stratification factors for the risk of cardiovascular complications in adolescents with exogenous-constitutional obesity of the first degree, are presented. 20 adolescents with exogenously-constitutional obesity of the 1st degree, 10 adolescents with overweight and 10 practically healthy adolescents with normal weight were examined. The results of the study confirmed that an increase in CRPhs, hypoadiponectinemia, and an increase in epicardial fat deposition in adolescents with exogenously-constitutional obesity of degree I are risk factors for the development of cardiovascular complications. A negative correlation of blood adiponectin level with CRPhs concentration and epicardial fat deposition thickness confirms the anti-inflammatory properties of adiponectin and its protective effect on the development of cardiovascular complications associated with obesity.

KEYWORDS: obesity, adolescents, highly sensitive CRPhs, adiponectin, epicardial fat thickness.

Relevance

To date, the problem of excess weight and obesity, as a factor that increases the risk of the formation of diseases of the cardiovascular system and diabetes mellitus, seems to be very relevant. Disappointing is the fact that a significant increase in the number of obese people is recorded all over the world, not only among adults, but also among children.

According to information provided by the World Health Organization, the number of overweight children is growing steadily throughout. Thus, the number of young children suffering from this ailment increased from thirty-two million in 1990 to forty-one million in 2016. These disappointing facts indicate that if such dynamics continue, then by 2025 the number of young children with overweight will increase to seventy million.[1]

The main causes of cardiovascular complications are obesity, type 2 diabetes, hypercholesterolemia, and arterial hypertension. It is obvious that the risks of cardiovascular pathology are formed in childhood, respectively, the steady increase in the number of overweight children is a harbinger of potential complications from the heart and blood vessels in adulthood. All this dictates the advisability of early detection and timely correction of the initial manifestations of cardiovascular lesions in obese children.[2]

Numerous studies have demonstrated that adipose tissue itself is one of the components of the pathogenesis of obesity, since it functions as an endo, auto and paracrine organ. Adipose tissue produces biologically active substances called adipocytokines, which can have a direct effect on the activity of metabolic processes in the tissues and systems of the body, and indirectly through the endocrine and humoral systems, entering into work with hormones of the pituitary, adrenal and pancreas.[3] Today it is known that obesity is accompanied by a disruption in the functioning of adipocytes, and the consequence of this dysfunction is an increased production of pro-inflammatory, and a decrease in the production of anti-inflammatory cytokines[4], the mechanisms of action of which are still being actively studied. Recent studies have shown that various adipocytokines, such as leptin and resistin, can contribute to morphofunctional remodeling of the heart, the development of dyslipidemia and the formation of insulin resistance and can participate in the regulation of vascular tone. Also, a number of scientific studies have demonstrated the protective properties of an adipocytokine such as adiponectin, which inhibits the adhesion of molecules to vascular endothelium, prevents the release of cytokines by macrophages and thereby blocks the formation of atherosclerotic plaques, which ultimately significantly reduces the risk of coronary heart disease.[5,6,7] The concentration of adiponectin in the blood decreases with obesity, mainly, with an increase in

the mass of visceral fat.[8] In an in vitro study, when adipocytes of subcutaneous and visceral adipose tissue were co-cultivated, a decrease in adiponectin secretion was noted, which indicates that visceral adipose tissue can produce substances that block adiponectin production and secretion.[9]

In addition, medical science is accumulating more and more evidence that adipose tissue is in a state of so-called aseptic inflammation.[10] Scientists have found that the greater the mass of visceral adipose tissue, the higher the level of systemic inflammatory response in the body. In a rodent experiment, it was clearly shown that the rapid rate of fat gain in rats with a normal initial weight led to a significant increase in the level of C-reactive protein and other pro-inflammatory cytokines (interleukin-6, tumor necrosis factor alpha). Moreover, the rate of weight gain was essential in the development of the intensity of the inflammatory reaction.[11]

The results of prospective studies of recent years have proved the error of verification of obesity only in terms of body mass index, as an indispensable factor that increases the risk of cardiovascular complications. Visceral fat deposition is the pathogenetic bridgehead for the formation of metabolic disorders, atherosclerosis and cardiovascular pathology. To better predict cardiometabolic risk, a direct assessment of visceral adipose tissue is necessary. The most accessible method for direct assessment of visceral adipose tissue is echocardiographic determination of the thickness of epicardial fat.[12]

Epicardial fat is a depot of visceral fat around the heart, concentrated between the myocardium and visceral pericardium. Moreover, it is a source of biologically active substances that affect the heart muscle and coronary arteries. Epicardial fat and myocardium, due to the lack of a fascia separating these structures, have a common microcirculation system and are supplied with branches of coronary arteries.[13] Epicardial adipose tissue produces a number of adipokines in the coronary bloodstream (adiponectin, interleukins - IL-1, IL-6, tumor necrosis factor a, visfatin, leptin, angiotensin, etc.), which affect metabolic processes in the myocardium in different ways and can cause clinico-metabolic and cardiovascular complications associated with visceral obesity.[14] In particular, interleukin 1, interleukin 6, tumor necrosis factor, free fatty acids, angiotensin II produced by adipose tissue from the vessels enter the artery wall, causing irreversible changes in it, which leads to the development of atherosclerosis. The above biologically active substances secreted by epicardial fat directly affect the vascular, immune and inflammatory reactions. Excess epicardial fat is also deposited along the coronary arteries, which turn out to be "chained" to the fat corset.[15] Under such conditions, all pro-inflammatory cytokines and adipokines are directly secreted into the coronary arteries, which provokes the rapid formation of atherosclerosis. In particular, the secretion of such an inflammatory mediator as tumor necrosis factor alpha can aggravate vascular inflammation, plaque instability due to apoptosis and pathological overgrowth of new vessels (neovascularization).[16] In addition, inflammatory mediators stimulate the flow of inflammatory cells into the walls of the arteries, spasm of the coronary vessels and micro-damage to the intima. At the same time, there is an opinion about the positive effects of the inflammatory reaction due to excess epicardial adipose tissue, namely activation of the angiogenic reaction and the development of collateral circulation in patients with obstructive coronary atherosclerosis.[17]

Epicardial fat has both positive and negative features, which are balanced under normal conditions, however, to date, the cause of the imbalance between them remains completely unexplored. Under normal physiological conditions, epicardial fat serves as an equilibrium system that absorbs excess toxic fatty acids. Increased production of the latter can lead to disorders in the formation and conduction of impulses in the conduction system of the heart and suggest the development of arrhythmias.[18]

The aim of the study was to evaluate the value of adiponectin, a highly sensitive C-reactive protein and the thickness of epicardial fat deposition as risk factors for the development of cardiovascular complications in adolescents with exogenous constitutional obesity of the first degree.

MATERIAL AND METHODS

The study was conducted on the basis of a teenage dispensary in Tashkent. The results of a survey of 40 adolescents are analyzed. The average age of the children included in the study corresponded to the teenage age and amounted to 15.4 ± 0.4 years, of which 20 were girls and 20 were boys. As a diagnostic criterion for overweight and obesity in children, we used the determination of the standard deviations of the body mass index. Based on WHO recommendations, adolescent obesity was defined as a body mass index equal to or more than +2.0 standard deviations of the body mass index, and overweight from +1.0 to +2.0 standard deviations of the body mass index. Normal body mass was diagnosed with body mass index values within 1.0 standard deviations of the body mass index. The subjects were divided into 3 groups: the main group - 20 adolescents with a primary constitutional-exogenous form of obesity of the 1st degree, the comparison group - 10 overweight children and the control group consisted of 10 normal weight children who did not have a history of obesity and associated with him complications. Physical and laboratory examination of patients was carried out. During the study, anthropometric parameters were determined: height, weight, waist and hips. Body mass index was calculated as the ratio of body weight in kilograms to the square of growth in meters (kg / m2).

The ratio of waist to hips was determined by dividing the waist circumference by the circumference of the hips.

To assess the thickness of epicardial fat, sizes and volumes of heart cavities, left ventricular myocardial mass index, systolic and diastolic functions of both ventricles, a standard transthoracic echocardiography study was performed in B and M modes on a PHILIPS ClearVue 350 apparatus. The EC was visualized as an echo negative space, the measurement of which was carried out on the free wall of the right ventricle.

The level of highly sensitive C-reactive protein (CRP-hs) was determined in blood serum using reagent kits from Siemens (Germany) on an Immulite 2000 instrument, Germany. For a reference level of CRP-hs, values of 0-3.0 mg / L are pleasant.

The concentration of serum adiponectin was determined by enzyme-linked immunosorbent assay using commercial BioVendor kits (Czech Republic) on a StatFax 2100 analyzer (Israel).

Exclusion Criteria

The study did not include patients with a secondary form of obesity: hypothalamic-pituitary (central) and dysfunctions of other endocrine glands (peripheral) forms.

The study was conducted in compliance with the ethical principles imposed by the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, 2013), and was performed with the informed consent of parents and patients. Statistical data processing was performed using the MS Excel for Windows 7 software. Statistical significance was determined using correlation analysis (Pearson method), at $p < 0.05$, differences were considered statistically significant.

RESULTS AND DISCUSSION

The average values of anthropometric indicators were: body mass index (kg / m2) in adolescents with obesity - 31.74 ± 0.73, overweight - 27.52 ± 0.96, in children with normal weight 22.51 ± 1, 32; waist circumference (cm) in adolescents with obesity - 98.32 ± 1.92, overweight - 90, 52 ± 1.86, in children with normal weight - 67.69 ± 2.77; hip circumference (cm) in adolescents with obesity - 106.59 ± 2.63, overweight - 100.39 ± 1.83, in children with normal weight - 90.69 ± 3.39; The ratio of waist to hip - in adolescents with obesity - 0.88 ± 0.02, overweight - 0.82 ± 0.03, in children with normal weight - 0.78 ± 0.03.

An analysis of an electrocardiographic study showed that among the subjects from the main and comparison groups: heart rhythm disturbances in the form of sinus tachycardia were recorded in 31.1% of children, sinus bradycardia - 3.3%, sinus arrhythmia - 13.3%, supraventricular extrasystole - in 5.5%, impaired automatism of the sinus node in the form of atrial rhythm in 13.3%, impaired conduction in the form of incomplete blockade of the right leg of the Giss bundle in 12%, and impaired repolarization processes in 33.3% of children. In the control group, there were no changes on the ECG.

To assess the structural state of the myocardium in adolescents with excess weight and obesity of degree I, a comparative analysis of morphometric and hemodynamic parameters was carried out according to ECHOCG with current control groups having normal weight (n = 10), as well as with their percentile values of healthy children and adolescents in depending on the surface area of the body (according to S. Vorobyov et al. 2015).[19]

It was found that in children with obesity and overweight, the average parameters of echocardiography were within optimal values, however, in relation to the control parameters, ultrasound parameters of the heart were higher. In particular, an increase of 33% in the thickness of the left ventricle is 0.95 ± 0.2 cm in the main group, versus 0.71 ± 0.05 cm in the control group, which may indicate an increase or / and expansion of the heart cavities due to volume overload (higher rates of end-systolic and diastolic sizes and volumes of the left ventricle).

Also, adolescents with obesity found additional signs of expansion of the heart chambers in the form of an increase in the diameter of the left atrium (3.08 ± 0.5 cm) and the right ventricle (2.76 ± 0.4 cm) in comparison with the control group 2.07 ± 0.9 cm and 1.45 ± 0.2 cm, respectively. It is likely that at this stage of structural and geometric myocardial rearrangement, the increase (expansion) of the left atrium and right ventricle are not true dilatation processes, but an element of primary adaptation (compensatory reaction) of the heart muscle, and / or these changes indicate initial (functional, potentially reversible)) signs of diastolic dysfunction in conditions of an increase in the volume of circulating blood accompanying obesity.

The indicators of central hemodynamics, reflecting the contractile and pumping functions of the heart, also differed in adolescents with obesity in comparison with the control group: the ejection fraction was 66.0 ± 4.9% versus 70.1 ± 2.2%, and the stroke volume was 80 , 4 ± 0.6 ml against 61.9 ± 5.6 ml.

In the comparison group, almost all of these indicators were higher than the echocardiographic parameters of normal-weight teenagers.

In adolescents with obesity, unlike children with overweight and normal weight, in whom epicardial fat was not visualized, during echocardiography on the front wall of the right ventricle, epicardial fat deposits from 2 to 5 mm thick were documented (average 2 ± 0.33 mm) – Fig 1.

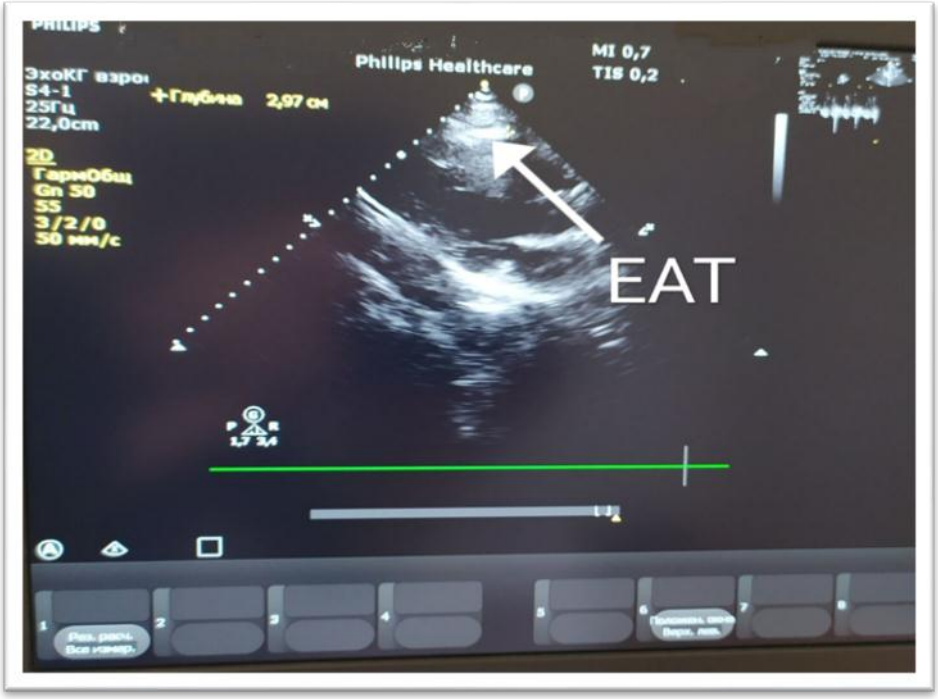

Figure 1: Echocardiogram of a boy U. 16 years old.

Diagnosis: Exogenously-constitutional obesity I degree. US-mode: left parasternal access, the long axis of the left ventricle, epicardial fat 5 mm thick is visualized.

Also, in the analyzed groups of adolescents, a comparative analysis of the levels of adiponectin and highly sensitive C-reactive protein (CRPhs) circulating in the blood plasma was performed. The analysis showed that the level of adiponectin in blood plasma in children was significantly different in the analyzed groups: in the group of children with obesity, adiponectin values were - 5.0 ± 0.13 μg / ml; in the group of overweight children - 7.5 ± 0.08 μg / ml, and in the group with normal weight - 15.3 ± 0.08 μg / ml. In adolescents with obesity and overweight, the level of the highly sensitive C-reactive protein is higher - 4.6 ± 0.06 mg / l in the group of obese children; 2.5 ± 0.04 mg / l - in the group of overweight children than in adolescents with normal weight - 0.9 ± 0.45 mg / l (Fig. 2).

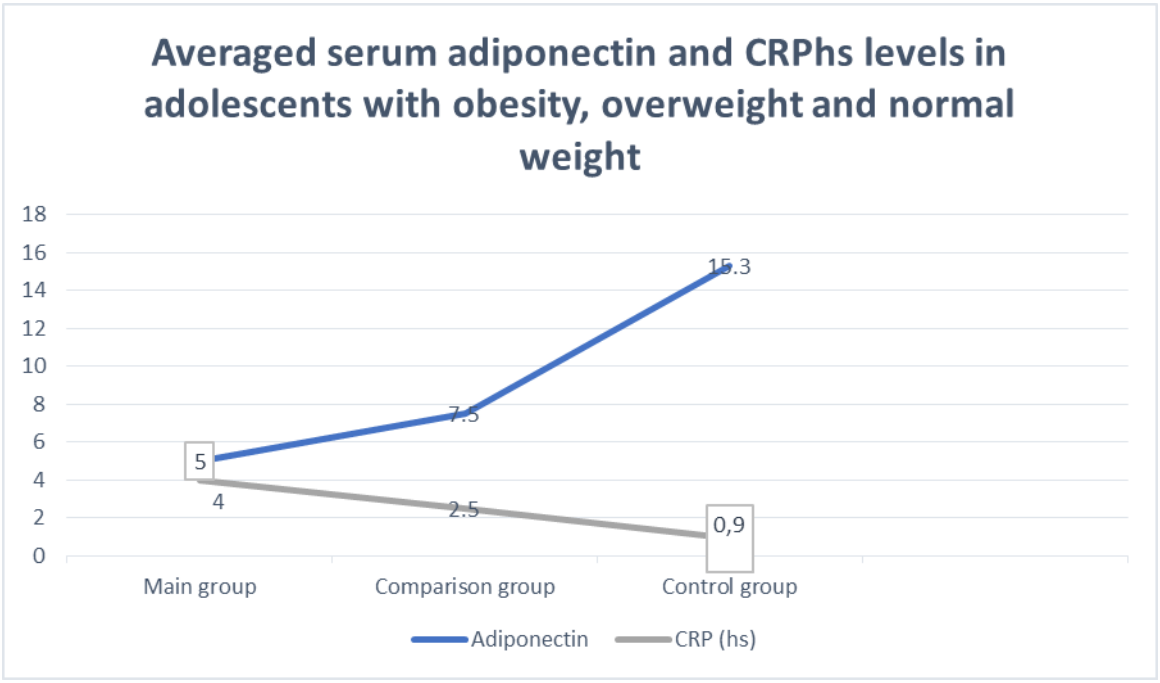

Figure 2.

The revealed higher level of CRPhs and low adiponectin in the group of adolescents with obesity and overweight is confirmed in many studies, which have proved the association of increased levels of CRPhs and hypoadiponectinemia with an increase in cardiovascular risk.[20] In one population-based study among Pima Indians, it was found that type 2 diabetes was less likely to develop in individuals with high adiponectin, unlike individuals with lower values.[21]

Some clinical studies have shown negative correlations between plasma adiponenctin values and cardiovascular diseases such as heart failure, myocardial infarction, atherosclerosis, and arterial hypertension.[22]

Thus, hypoadinectinemia in visceral obesity may play a key role in the formation and progression of complications associated with obesity - type 2 diabetes mellitus and cardiovascular disease.

To obtain more complete information about the features of the relationship between the studied parameters, we performed a correlation analysis, which revealed a positive correlation of CRPhs concentration with body mass index (g = + 0.610 p <0.01) and epicardial fat thickness (g = 0.845 p <0.001), and the inverse correlation of adiponectin with body mass index (g = -0.546 p <0.05) and epicardial fat thickness (g = -0.741; p <0.001) Fig. 3.

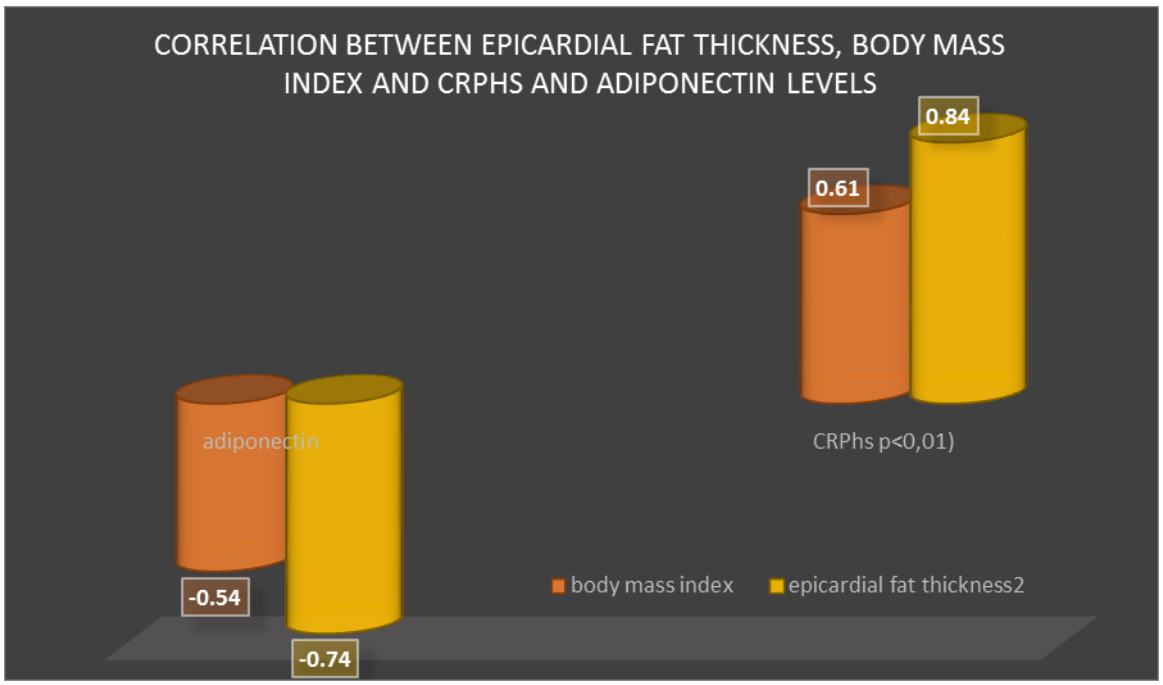

Figure 3.

The nature of the obtained relationships allows us to make an assumption about the influence of the degree of epicardial fat deposition and the activity of the inflammatory process on subclinical damage to the cardiovascular system, which, if untimely corrected, can lead to the development of cardiovascular catastrophes in the future. The revealed negative correlation of adiponectin level with CRPhs and epicardial fat thickness proves its anti-inflammatory properties and protective effect on the cardiovascular system as a whole, which coincides with published data.[23,24,25]

CONCLUSIONS

1. In adolescents with exogenously-constitutional obesity of the 1st degree, an increase in the level of CRPhs, hypoadinectinemia and an increase in the thickness of epicardial adipose tissue more than 2 mm can be considered as independent risk factors for the development of cardiovascular complications.
2. Echocardiographic signs of enlargement of the heart chambers in adolescents with overweight and exogenously constitutional obesity of the first degree, compared with the control group, are obviously elements of the primary adaptation of the heart muscle in the face of an increase in the volume of circulating blood accompanying obesity, and with timely correction are potentially reversible.
3. A negative correlation of the level of blood adiponectin with the concentration of highly sensitive CRPhs and the thickness of the epicardial fat deposition indicates the anti-inflammatory properties of adiponectin and its protective effect on the development of cardiovascular complications in adolescents with exogenous constitutional obesity of the 1st degree.
4. To assess the prognosis of the development of cardiovascular complications, it is advisable to include in the examination program for adolescents with exogenously-constitutional obesity grade I the determination of the level of CRPhs, blood adiponectin,

and epicardial fat deposition thickness indices according to echocardiography.

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