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ABSTRACT

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DETERMINATION OF CERTAIN INTEGRAL PARAMETERS ASSOCIATED WITH ARTERIAL HYPERTENSION IN OBESE CHILDREN

The aim of the study: Stratification of integral indicators determining the risk of developing arterial hypertension in obese children.

Materials and methods. The observation group consisted of 139 obese children aged 11–17 years, who were divided into two subgroups depending on the level of blood pressure (BP). The first subgroup included 50 (36 %) adolescents with obesity and hypertension. The second subgroup consisted of 89 (64 %) children with normal blood pressure. The comparison group consisted of 36 conditionally healthy children, representative of age and gender.

To identify the least possible number of latent common factors that have the greatest impact on the development of hypertension in obese children and determine their factor loadings, factor analysis by the principal component method was used, followed by orthogonal VARIMAX rotation of the factor axes. Significant factors in the model were examined using the scree-test and the Kaiser criterion, followed by the identification of indicators with a high factor loading on the complex (over 0.6).

Results. Using factor analysis, 4 significant factors were identified, the dispersion of which determined 79.23 % of the contribution of all factors: 1) the factor of carbohydrate metabolism disorders, which included fasting glucose, the insulin sensitivity index QUICKI, and the insulin resistance index HOMA; 2) biological factor (gender and age of the child); 3) autonomic regulation factor (circadian heart rate index); 4) metabolic factor, which includes body mass index, waist-to-height ratio and serum cortisol level. It has been proved that hyperinsulinemia and insulin resistance are the leading factors contributing to the development and progression of hypertension in obese children.

Conclusions. The obtained factor model will allow optimizing approaches to preventing the development and progression of

hypertension in obese children by identifying a risk group for the development of arterial hypertension, taking into account the identified factors.

Keywords: obesity, arterial hypertension, insulin, insulin resistance, risk factors, factor analysis, children.

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ВИЗНАЧЕННЯ ДЕЯКИХ ІНТЕГРАЛЬНИХ ПОКАЗНИКІВ, ЩО ОБУМОВЛЮЮТЬ РОЗВИТОК АРТЕРІАЛЬНОЇ ГІПЕРТЕНЗІЇ У ДІТЕЙ, ХВОРИХ НА ОЖИРІННЯ

Мета роботи – стратифікація інтегральних показників, що визначають ризик розвитку артеріальної гіпертензії у дітей, хворих на ожиріння.

Матеріали і методи. Групу спостереження склали 139 дітей, хворих на ожиріння, віком 11–17 років, які були розподілені на дві підгрупи в залежності від рівня артеріального тиску (АТ). До першої підгрупи увійшло 50 (36 %) підлітків з ожирінням та артеріальною гіпертензією. Другу підгрупу склали 89 (64 %) дітей з нормативними показниками АТ. Групу порівняння склали 36 умовно здорових дітей, репрезентативних за віком та статтю.

Для виявлення як щонайменшої кількості прихованих загальних факторів, що найбільш впливають на розвиток артеріальної гіпертензії у дітей, хворих на ожиріння, застосовувався факторний аналіз методом головних компонент з подальшою ортогональною VARIMAX - ротацією факторних осей. Значущі фактори в моделі досліджували за допомогою критерію «кам'янистого осипу» та критерію Кайзера з подальшим визначенням показників з високим факторним навантаженням на комплекс (понад 0,6).

Результати. За допомогою факторного аналізу було виділено 4 значущі фактори, дисперсія яких визначала 79,23 % від вкладу усіх факторів: 1) фактор порушення вуглеводного обміну, який включав вміст глюкози натщесерце, індекс чутливості до інсуліну QUICKI, індекс інсулінорезистентності HOMA; 2) біологічний фактор (стать і вік дитини); 3) фактор вегетативної регуляції (циркадний індекс ритму серця); 4) метаболічний фактор, в склад якого увійшли індекс маси тіла, показник співвідношення обводу талії до росту дитини та вміст кортизолу в сироватці крові. Доведено, що провідним фактором, що сприяє розвитку та прогресуванню артеріальної гіпертензії у дітей, хворих на ожиріння, виступає гіперінсулінемія та резистентність до інсуліну.

Висновки. Отримана факторна модель дозволить оптимізувати підходи до профілактики розвитку та прогресування артеріальної гіпертензії у дітей, хворих на ожиріння, шляхом виділення групи ризику з розвитку артеріальної гіпертензії з урахуванням виділених факторів.

Ключові слова: ожиріння, артеріальна гіпертензія, інсулін, інсулінорезистентність, фактори ризику, факторний аналіз, діти.

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ABBREVIATIONS

HRV – heart rate variability
HR – heart rate
WHR – waist and hip ratio
BMI – body mass index
WHtR – waist to height ratio
BP – blood pressure
CI – circadian index

INTRODUCTION

Obesity, which has become a major epidemic in the 21st century, is associated with a high incidence of cardiovascular complications [1]. Obesity rates have been steadily increasing among children over the past few decades. It is expected that by 2050, obesity will affect 25 % of children worldwide if current trends continue [2]. This epidemic is accompanied by an increase in the prevalence of childhood hypertension and does not depend on the country's economic level [3]. It has been proven that being overweight at a young age increases the risk of developing primary arterial hypertension by up to 75 % [1]. Among obese children, the prevalence of hypertension is up to 30 %, while among the pediatric population with normal weight it is less than 3-5 % [4].

Although diseases such as stroke or myocardial infarction are the domain of adult life, numerous studies have shown that pathological processes of the cardiovascular system, including hypertension, which begin in childhood, contribute to an increased risk of adverse cardiometabolic events in adulthood [5]. Despite the fact that the causal relationship between obesity and high blood pressure is well established, its detailed mechanisms are still being studied. Therefore, identifying risk factors for developing hypertension in obese children at early stages, when these processes are still reversible, and developing preventive strategies are key to reducing cardiovascular morbidity and mortality in the population as a whole.

The aim of the study. Stratification of integral indicators determining the risk of developing arterial hypertension in obese children.

MATERIALS AND METHODS

The study group consisted of 139 obese children aged 11–17 years (mean age 13.6 ± 0.2 years) who were treated in the endocrinology department of the Municipal non-commercial enterprise of Zaporizhzhia Regional Council «Zaporizhzhia Regional Children's Clinical Hospital». The diagnosis of obesity in adolescent children was based on the results of body mass index calculation. The presence of obesity was assessed using a body mass index (BMI in kg/m^2) exceeding 2 standard deviations above the Growth Reference median according to WHO recommendations [6]. The type of fat deposition was analyzed by the waist and hip ratio (WHR) and waist to height ratio (WHtR). The diagnosis of arterial hypertension was verified according to the criteria for diagnosing this pathology in children [7,8]. Depending on the level of blood pressure (BP), obese children were divided into two subgroups. The first subgroup included 50 (36%) adolescents with obesity and elevated "office" BP at or above the 95th percentile. The second subgroup consisted of 89 (64 %) adolescents with obesity and normal blood pressure for their age, height and sex. The control group included 36 adolescent children without signs of obesity and arterial hypertension, who did not differ in age and sex from the children in the observation group and had no intervening diseases at the time of the examination.

All children underwent a standard examination, which includes anamnesis, physical examination, and laboratory-instrumental examination.

Insulin resistance was calculated using the fasting HOMA index (HOMA-IR) [9], and insulin sensitivity was estimated using the Quantitative Insulin Sensitivity Check Index (QUICKI) [10].

Holter monitoring of cardiac activity was performed using the "Cardiosens+" hardware and software complex (XAI-MEDICA, Kharkiv, Ukraine) with subsequent assessment of heart rate variability (HRV) with a complete analysis of HRV parameters in the modes of time and spectral analysis, using the circadian index (CI) as a ratio of mean daily heart rate (HR) to mean nightly HR.

Insulin and cortisol levels were measured using commercial enzyme-linked immunosorbent assay kits (Insulin ELISA, DRG Germany and Cortisol EIA-1887, DRG, USA).

To identify the least possible number of latent common factors that have the greatest impact on the

development of hypertension in obese children and determine their factor loadings, factor analysis by the principal component method was used, followed by orthogonal VARIMAX rotation of the factor axes. The basis for modelling the selection of factor complexes was the Spearman correlation matrix with the subsequent determination of the burden vector of the studied indicators. Significant factors in the model were examined using the screen-test and the Kaiser criterion, which eigenvalues were more than 1.0, followed by the identification of indicators with a high factor loading on the complex (over 0,6). Factor analysis using the VARIMAX rotation was performed taking into account the results of the initial analysis and using principal components to describe the dispersion of the data set.

The results of the study were processed using the statistical licensed software package Statistica for Windows 13.0, serial number JPZ804I382130ARCN10-J, and SPSS 23.0 for Windows. For all types of analysis, differences at $p<0.05$ were considered statistically significant.

All studies conducted complied with the ethical standards of the Institutional and National Research Committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

RESULTS

According to the results of multivariate analysis of the set of medical, biological and clinical laboratory relationships, by the method of sequential selection, 10 variable parameters were identified, which made up the dispersion of 11 factors and determined the likelihood of developing arterial hypertension in obese children, in particular: gender, age, body mass index, waist-to-height ratio, fasting blood glucose, insulin resistance and insulin sensitivity indices, serum cortisol, and circadian heart rate index.

Using the varimax orthogonal rotation, the first 4 consecutive significant factors were identified, the total contribution to the dispersion of which determined 79.23% of the content of all factors (Table 1).

Table 1 – Eigenvalues of the factors and their percentage in the total dispersion

Factor	Initial eigenvalues			Rotation of the sum of squared loads		
	Total	% of dispersion	Total %	Total	% of dispersion	Total %
1	4.255	38.68	38.68	3.919	35.63	35.63
2	1.757	15.97	54.65	1.739	15.81	51.44
3	1.517	13.79	68.44	1.529	13.90	65.34
4	1.186	10.78	79.22	1.528	13.89	79.23
5	0.907	8.25	87.47			
6	0.676	6.15	93.62			
7	0.447	4.06	97.68			
8	0.160	1.46	99.14			
9	0.084	0.76	99.90			
10	0.010	0.09	99.99			
11	0.001	0.01	100.000			

During the analysis of factor loadings, it was found that the greatest contribution to the development of hypertension in obese children was made by the “carbohydrate metabolism disorder factor”, the total contribution of which to the total informativeness was 36.63% (Table 2).

This factor was distributed among several components: fasting glucose (factor loading of 0.935), insulin sensitivity index QUICKI (factor loading of 0.983) and insulin resistance index HOMA (factor loading of -0.826).

The second factor, named “biological”, was distributed between two parameters: gender and age of the child (factor loadings of 0.646 and 0.879, respectively). This factor is unadjusted and its contribution to the total variance was 15.81%.

In the third factor of the matrix with a proportion of variance of 13.90% and a factor loading of 0.956, only one variable was identified - the circadian heart rate index (CI). The identified factor was interpreted by us as the “autonomic regulation factor”.

The group factor of the fourth rank, which accounted for 13.89% of the dispersion, included factors that should be interpreted as a “metabolic factor”. In this group, there were 3 initial risk factors that had the highest factor loadings: body mass index (factor loading of 0.671), waist-to-height ratio (factor loading of -0.670), and serum cortisol (factor loading of 0.631).

Table 2 – Matrix of factor loadings

Parameter	Factor			
	1	2	3	4
Insulin	-0.485	0.498	0.433	-0.279
Gender	0.389	**0.646**	-0.271	0.136
Age	-0.038	**0.879**	0.064	-0.091
BMI	0.141	0.310	-0.176	**0.671**
Cortisol	-0.102	-0.104	0.484	**0.631**
Glucose	**0.935**	0.191	0.055	0.224
HOMA	**-0.826**	0.300	0.276	0.177
QUICKI	**0.983**	0.049	-0.053	0.138
WHtR	-0.196	0.224	0.054	**-0.670**
CI	-0.010	-0.025	**0.956**	-0.048

The results of factor loadings analysis revealed that the components of all four factors had close correlations with insulin levels (Fig. 1).

Thus, based on the results of the correlation analysis, it can be concluded that the leading factor that plays a major role in the development of hypertension in obese children is elevated insulin levels.

DISCUSSION

The use of factor analysis allowed us to identify and interpret individual factors in the formation of hypertension in obese children.

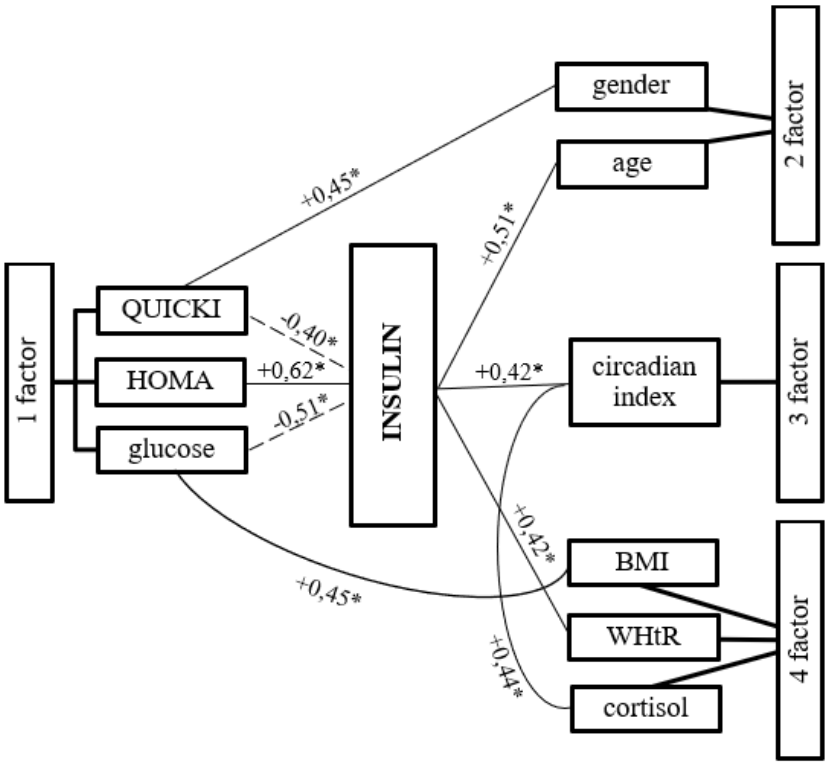

Figure 1 – Correlations between the components of the selected factors and insulin in children with obesity and hypertension

Note: * $p < 0.05$

——— – direct correlation

– – – – – – inverse correlation

According to the results of the study, hyperinsulinaemia and insulin resistance are the leading factors contributing to the development and progression of hypertension in obese children. This assumption is supported by our data on insulin levels in the blood serum of obese children. While in patients without arterial hypertension the insulin level was not statistically different from the control group and amounted to 13.48±0.92 μU/l versus 11.28±1.44 μU/l, respectively (p>0.05), whereas in children with obesity and arterial hypertension the insulin content was determined in the range of 20.70±1.86 μU/l, which was significantly higher than its value in the control group and in the group of obese children without arterial hypertension (p<0.05). Simultaneously with the increase in insulin level in children with obesity complicated by the development of arterial hypertension, there was a significant increase in the HOMA index (3.69±0.51 units vs. 2.39±0.15 units in the group of patients without arterial hypertension and 2.04±0.25 units in the control group, p<0.05) and a decrease in insulin sensitivity (1.41±0.03 units vs. 1.51±0.03 units and 1.61±0.05 units, respectively, p<0.05).

The obtained results are in line with the current understanding of the pathogenetic mechanisms of hypertension, which indicate that these two factors are among the most important factors contributing to obesity-related blood pressure [11]. Today, insulin resistance is getting more and more common in children and adolescents [12]. Several studies have shown that hypertension and insulin resistance are closely related and causally related [1,11]. There is an assumption that hyperinsulinemia and insulin resistance may precede the development of hypertension. In a meta-analysis by F. Wang et al. (2017) demonstrated that elevated fasting insulin levels or insulin resistance, quantified by HOMA-IR, correlate with an increased risk of developing hypertension in the general population [13]. There was also a strong association between changes in glucose levels and high systolic blood pressure (factor loading +0.935). Another study, conducted in children, recently demonstrated that fasting glucose and insulin levels gradually increased according to the stages of hypertension in children [14], which is consistent with our results.

It has been established that in determining the risk factors of hypertension in obese children, it is mandatory to take into account such unmodified factors as the age and gender of the child. Our study demonstrates that serum insulin levels in obese children increased with age (r = +0.51, p<0.05) and were independent of body mass index (r = +0.19, p > 0.05), reflecting the increase in insulin levels with the onset of puberty. This is consistent with the results of other studies showing that pubertal development is associated with a physiological decrease in insulin sensitivity due to a compensatory increase in insulin secretion. However, while in children with normal weight insulin sensitivity is restored at the end of puberty, in obesity full restoration of sensitivity to this hormone does not occur and, moreover, more pronounced insulin resistance remains at all stages of puberty [15].

Numerous studies have convincingly demonstrated gender differences in the prevalence and development of insulin resistance, which is generally more prevalent in men than in women [16]. The data of our study show that insulin sensitivity, which was determined by the QUICKI index, was higher in girls than in boys (r = -0.51, p<0.05). Our results are consistent with those of I. Aldhoon-Hainerová et al. (2014), who showed that obese boys were more likely to show hyperinsulinemia and insulin resistance than obese girls [17].

The third factor that influenced the development of hypertension in obese children and depended on insulin synthesis was the “vegetative factor”. Under the influence of hyperinsulinemia, the sympathetic autonomic nervous system was activated, which led to an increase in the circadian heart rate index (r = +0.42, p<0.05). Our findings are in agreement with a number of studies that have shown that obesity is associated with a decrease in cardiac parasympathetic activity in children [18]. It is known that excessive sympathetic activity in obesity causes activation of the renin-angiotensin-aldosterone system (RAAS), which leads to sodium and water retention and, as a result, increased blood pressure [19]. In turn, RAAS are involved in the pathogenesis of obesity and insulin resistance and directly affect adipocyte physiology by modulating lipid storage capacity, inflammatory phenotype and, as a result, insulin sensitivity [14,20]. Considering these data, hypersympathicotonia and pronounced activation of the RAAS in obese children may contribute to the development of insulin resistance [11].

The fourth group of factors that contributed to the development of hypertension in obese children included BMI > 97th percentile, visceral obesity, and elevated serum cortisol levels. Even a slight increase in visceral fat volume and waist circumference, which is considered a sign of visceral obesity, is a marker of metabolic disorders and the development of cardiovascular disease [21,22]. In children and adolescents, visceral obesity can also better predict cardiometabolic risk factors than BMI alone and is considered an independent risk factor of hypertension [23]. It has been proven that an increase of BMI by 1.7 kg/m2 or waist circumference by 4.5 cm is associated with an increase in systolic blood pressure by 1 mmHg [24]. On the other hand, morbid obesity is accompanied

by adipose tissue dysfunction due to its lipid overload, which increases the risk of metabolic complications, including insulin resistance, and increases the risk of arterial hypertension [25].

It is known that insulin resistance is one of the main triggering factors of metabolic disorders in obesity [26]. The main hormone associated with excessive weight gain and hypertension, which is involved in metabolic dysregulation, is cortisol, which can be hypersecreted by the adrenal cortex as a result of chronic activation of the sympathetic nervous system [18]. According to our study, children with obesity and hypertension demonstrated increased cortisol production. We found a positive correlation between serum cortisol levels in obese children and the circadian heart rate index ($r = +0.44$, $p < 0.05$), which confirms the role of the sympathetic nervous system in stimulating cortisol production. To date, it has been proven that cortisol produced in adipose tissue can stimulate renin production, similar to aldosterone and can also increase insulin resistance [27]. However, the mechanisms that trigger the activation of cortisol synthesis in obesity are not yet completely known [18].

Thus, the results of the factor and correlation analyses made it possible to identify a certain clinical and laboratory phenotype, which is inherent in children with obesity and hypertension: hyperinsulinemia and insulin resistance; metabolic abnormalities and modified body composition; activation of the sympathetic autonomic nervous system; arterial hypertension. These changes are similar to those observed in adults with hypertension and obesity [28]. Therefore, weight loss and prevention of insulin resistance by identifying and modifying risk factors is a priority for the primary prevention of hypertension in obese children [29].

Thus, the factor analysis made it possible to identify the main pathogenetic mechanisms and their factor relationships that have the greatest impact on the development and progression of hypertension in obese children.

CONCLUSIONS

1. The results of the study have revealed some pathogenetic factors in the development of arterial hypertension in obese children. The priority contribution to the development of arterial hypertension is made by impaired insulin sensitivity (factor loading of 0.983), insulin resistance (factor loading of -0.826), gender (factor loading of 0.879) and age (factor loading of 0.646) of the child, hypersympathicotonia (factor loading of 0.956), hypercortisolemia (factor loading of 0.631) and visceral obesity (factor loading of -0.670).
2. The obtained factor model will allow optimizing approaches to preventing the development and progression of hypertension in obese children by identifying a risk group for the development of arterial hypertension, taking into account the identified factors.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

To create a mathematical model for predicting the development of arterial hypertension in obese children to identify patients at high risk of developing this complication and to conduct timely diagnostic, therapeutic and preventive measures.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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None.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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