MUNTEANU DIANA [1,2], HLISTIN VICTORIA [1], RIZOV CRISTINA [2], VUDU LORINA [2], UȘURELU NATALIA [1]

THE METABOLIC IMPACT OF PRIMARY CHILDHOOD OBESITY

1-Institute of Mother and Child, Chisinau, Republic of Moldova
2- State University of Medicine and Pharmacy, "Nicolae Testemițanu", Chisinau, Republic of Moldova

REZUMAT

IMPACTUL METABOLIC AL OBEZITĂȚII PRIMARE LA COPIL

Cuvinte cheie: Obezitate, copii, impact metabolic.

Introducere: Obezitatea infantilă este considerată cea mai frecventă patologie cronică la copii și adolescenți, afectând fiecare grupă de vârstă. Constituind o tulburare cronică a stării de nutriție, caracterizată prin creșterea greutății corporale datorată țesutului adipos, obezitatea este însoțită și de dereglarea verigilor evidente ale metabolismului glucidelor, lipidelor și proteinelor și a riscului metabolic și cardiovascular pe termen lung. O abordare terapeutică și o intervenție eficientă și cât mai curând posibil la copiii cu modificări metabolice, previne instalarea complicațiilor ireversibile la vârsta de adult.

Materiale și metode: Materiale și metode. Studiul a inclus 100 de copii, cu vârste cuprinse între 6 - 18 ani, raportul dintre fete: băieți este 1: 2, cu participare liber consimțită. Au fost înregistrate măsurătorile antropometrice și rezultatele examinării. După 10 orede post alimentar, a fost prelevat sângele pentru evaluarea profilului lipidic, insulinei serice, glicemiei și enzimelor hepatice. Testul oral de toleranță la glucoză s-a făcut cu 1,75 g / kg glucoză Steatoza hepatică a fost estimată prin evaluarea modificărilor caracteristice la ultrasonografie și nivelul crescut de ALT.

Rezultate și discuții: Au fost studiați 100 de copii. Diverse tulburări cauzate de creșterea în greutate au fost detectate la majoritatea copiilor înscriși în studiu. Toți pacienții au avut CA (circumferința abdomenului) > percentila 98. Conform criteriilor propuse de IDF (Federația Internațională a Diabetului), în 47,5% cazuri a fost confirmat SM (sindrom metabolic) și în 31,6% cazuri cu factori de risc pentru acesta. Steatoza hpatică a fost confirmate în 34%. Profilul lipidic modificat și riscul aterogen crescut Profilul lipidic a celor 100 de copii examinați a exprimat diferite abateri, astfel încât în 27% există valori crescute ale colesterolului, valori ale LDL> 150.

Concluzii: Obezitatea primară la copii implică un risc metabolic crescut și necesită o abordare terapeutică li intervenție cât mai curând posibil, pentru a preveni instalarea unor compicații ireversibile la vârsta de adult.

РЕЗЮМЕ

МЕТАБОЛИЧЕСКОЕ ВОЗДЕЙСТВИЕ ПЕРВИЧНОГО ОЖИРЕНИЯ У ДЕТЕЙ

Ключевые слова: ожирение, дети, метаболическое воздействие.

Введение. Детское ожирение считается наиболее частой хронической патологией у детей и подростков, поражающей все возрастные группы. Являясь хроническим нарушением питания, характеризующимся увеличением массы тела из-за жировой ткани, ожирение сопровождается нарушениями очевидных звеньев углеводного, липидного и белкового обмена и долгосрочным метаболическим и сердечно-сосудистым риском. Раний терапевтический подход и эффективное вмешательство у детей с метаболическими изменениями предотвращают возникновение необратимых осложнений во взрослом возрасте.

Материалы и методы: В исследование были включены 100 детей в возрасте от 6 до 18 лет, соотношение девочек: мальчиков 1:2, при свободном согласии. Фиксировались антропометрические измерения и результаты обследований. После 10 часов голодания был произведен забор крови для оценки липидного профиля, сывороточного инсулина, глюкозы в крови и ферментов печени. Тэст на толерантность к глюкозе проводился с 1,75 г / кг глюкозы. Стеатоз печени оценивался путем оценки характерных изменений на УЗИ и повышенных уровней АЛТ.

Результаты и обсуждения: Обследовано 100 детей. У большинства детей, включенных в исследование, были выявлены различные нарушения, вызванные увеличением веса. У всех пациентов был АЖ (окружность живота)> 98 перцентиля.Согласно критериям, предложенным МФД(Международная федерация диабета), в 47,5% случаев был подтвержден РС (метаболический синдром), а в 31,6% случаев - с факторами риска этого заболевания. Стеатоз печени подтвержден у 34%. Изменения липидного профиля и повышенный риск атерогенности. Липидный профиль 100 обследованных детей выражал различные отклонения, так что у 27% наблюдались повышенные значения холестерина, значения ЛПНП> 150.

Выводы. Первичное ожирение у детей связано с повышенным метаболическим риском и требует терапевтического подхода и как можно ранего вмешательства, чтобы предотвратить возникновение необратимых осложнений во взрослом возрасте.

Introduction. Childhood obesity is considered one of the most alarming public health issue. As prevalence of childhood obesity rises, its healyh implication becomes more evident. Obesity is correlated with significant health problems in children and represent an early risk factor for much of adult morbidity and mortality. Particularly, childhood obesity tends to keep on to adulthood and thus represents an early beginning of a potentially life time pathological process. [1,2]. Most of the metabolic and cardiovascular complications of obesity are caused during childhood and are closely associated to the presence of insulin resistance/hyperinsulinemia, with the most common abnormality associated with obesity. The obesity-related morbidities that appear early in childhood are an alteration in glucose metabolism and fatty infiltration of the liver (nonalcoholic fatty liver disease [NAFLD]). Also an accelerated atherogenic process is present, the clinical manifestations of cardiovascular disease do not emerge during childhood. The diffilulty of diagnosis and risk assessment arises because both impaired glucose tolerance (pre-diabetes) and NAFLD are conditions with no clinical manifestations, and their diagnosis depends on the right choice of screening and diagnostic tests.

Metabolic syndrome (MS) is a latest medical problem, considered one of the most important causes of cardiovascular morbidity and mortality. A meta-analysis of large population studies, demonstrate that MS causes a 27-37 % increase in the risk of total mortality and 65-93 % risk of cardiovascular disease. Metabolic syndrome consists of several disorders and is attested if at least 3 of the following are present: hypertension, abdominal obesity, insulin resistance and dyslipidemia. To the described complex can be added: proinflammatory and prothrombotic state, non-alcoholic hepatic steatosis and sleep apnea [4,16].

Unhealthy diet, sedentary lifestyle, urbanization represent the major factors of increasing the number of children with metabolic syndrome. The predisposing factors for the lifestyle that lead to the appearance of metabolic syndrome are found both in the family (most children with metabolic syndrome, having obese relatives in the family or with metabolic syndrome), and in society (development of fast food networks, increasing time spent in in front of the computer or TV, lack of physical activity) [7].

Evidence shows that a combination of dietary interventions, behavioral therapy, and exercise is a significant impact in reducing the number of children with metabolic syndrome. Therapeutic intervention targets all components of metabolic syndrome

Materials and Methods. A prospective observational study was conducted that included 100 overweight children, that were referred to the Endocrine Department of the IMSP Mother and Child Institute, Chisinau, Republic of Moldova. Each child was examined and the findings were recorded The anthropometric parameters were assessed: height, weight, abdominal circumference, (CA), hip circumference, BMI (weight / height2). Patients were selected based on the following criteria: age of children 6-18 years, children with BMI> 95% percentile, children with AC> 95% percentile, children with primary obesity, lack of mental retardation, agreement to participate in the study. The control group consisted of 100 children of normal weight. Each child completed the questionnaire that provided information about eating habits, physical activity, psycho-social aspects, such as relationships with loved ones, family entourage, self-esteem assessment.

Blood was taken fter 10-hour overnight fast for evaluation of lipid profile, serum insulin, blood glucose and liver enzymes AST and ALT. The oral glucose tolerance test was done with 1,75 g/kg glucose to maximum 75 gr. Fatty infiltration of the liver was estimated by evaluation of particular features on ultrasonography NASH (non-alcoolic steatohepatitis) was defined as fatty infiltration of the liver wih higl level of ALT.

Weight, height and waist circumference were calculated. The weights and heights of the patients were measured accordind to standard practice using an electronic weighing scale and a wall mounted stadiometer. The waist circumference, that is an indicator of central obesity, was measured in the horizontal plane midway between the

costal margin and the iliac crest in the mild-axillary line. Fatty infiltration of the liver was assessed using ultrasonography and graded according to ultrasonic appearance of three features: liver echo texture, liver diaphragm differentiaton in echo amplitude with the hepatic echo penetration and clarity of liver blood vessels.

Results and discussion. A currently growing number of obese children and the concomitant increase of type 2 diabetes in young people emphasize the importance of acknowledging that pediatric MS is related to greater risks for the development of type 2 diabetes and cardiovascular diseases (CVD) at a later age.

Many of the metabolic and cardiovascular (CV) complications of obesity begin in infancy and are closely linked to the development of insulin resistance, which leads to hyperinsulinemia, the most common biochemical abnormality associated with obesity.

G.M. Reaven first described the concept of MS in 1988, presuming it played a core role in the development of CVD, mainly through insulin resistance of target tissues. NHANES III (Third National Health and Nutrition Examination Survey), 1988–94 was the first to reveal that 4.2 % of adolescents in general, and almost 30 % of overweight and obese adolescents in the US met the criteria for MS diagnosis. The 1999-2000 NHANES identified a further increase of MS among US adolescents, from 4.2 % (NHANES III, 1988–94) to 6.4 % (NHANES 1999–2000). The incidence of MS was exclusively high among overweight adolescents.

Initially, as far as adults were concerned, MS was defined as the clustering of obesity and associated factors of cardiometabolic risk, this leading plainly to increased risk of type 2 diabetes and CVD. The main factors were abdominal obesity, glucose intolerance, dyslipidemia (elevated triglyceride (TG), reduced high-density lipoprotein (HDL) associated with hypertension). The insulin resistance (IR) was a key pathophysiological mechanism that connected the elements mentioned above.

Insulin resistance, in its broadest sense, refers to a reduction in whole-body glucose absorption in response to physiologic insulin levels, as well as its effects on glucose and insulin metabolism. It is now apparent, though, that not all tissues are similarly insulin resistant. Global metabolic disorder, such as leprechaunism or Rabson-Mendenhall syndrome, would arise from generalized insulin resistance. As a result, obesity-related insulin resistance would quantitatively affect multiple tissues.

There is no universally accepted definition of MS in children and adolescents. To identify risk factors associated with MS, multiple pediatric studies used a variety of variables, parameters, and cut-off points. Most definitions of pediatric MS, on the other hand, disregard changes in the hormonal status that arise during childhood and adolescence, such as the developmentally-related rise in insulin secretion, pubertal changes in fat and fat-free mass, and changes in growth hormone and sex steroid secretion during puberty.

One of the most widely accepted definitions can be found in the International Diabetes Federation (IDF) group's 2007 consensus report. There are three age ranges in this definition: 6 to 10, 10 to 16, and >16 years (adult criteria). Obesity is defined as waist circumference (WC) ≥90th percentile, or adult cut-off if lower, in the IDF consensus report, while all other parameters are expressed in absolute numbers rather than percentiles. Since clinical, biochemical, and hormonal values are highly inconsistent and rely on maturation stages throughout childhood and adolescence, absolute numbers rather than percentiles are used for cut-offs. The absolute cut-offs are as follows: ≥150 mg/dL for triglycerides (or specific treatment for triglycerides), <40 mg/dL for HDL and <50 mg/dL in females over the age of 16 (or specific treatment for HDL), ≥130 mmHg for systolic and ≥85 mmHg for diastolic blood pressure (or treatment of previously diagnosed hypertension) and fasting plasma glucose ≥100 mg/dL or known type 2 diabetes.

The stability of MS diagnosis during adolescence has been studied in more recent research. Epidemiological studies revealed that, while the clustering of metabolic risk factors was consistent, the categorical diagnosis of MS was not stable during adolescence. The concepts used to support the usefulness of MS diagnosis in the young people may differ by maturation, according to research that examined the accuracy of three alternative models of MS factor structure across three developmental transitions. As a result, they are not suitable for the pediatric population. These studies show a high degree of MS diagnostic variability during puberty, implying that defining MS might not be appropriate for identifying risk in children and adolescents. As a result, physicians should concentrate their attention on promoting a healthier lifestyle and preventing obesity rather than focusing on complex hormonal and biochemical changes.

Table 2

The IDF consensus definition of metabolic syndrome in children and adolescents

Age (years)	Waist circumference (WC)	Blood Pressure (BP)	Glucose (mmol/l)	Triglicerydes	HDL-colesterol
6-<10	≥ percentile 90	Metabolic syndrome cannot be diagnosed, but further measurements should be made if there is a family history of metabolic syndrome, T2DM, dyslipidemia, cardiovascular disease, hypertension and/or obesity			
10-<16	≥ percentile 90	-Systolic ≥130/ diastolic ≥85 mm Hg	≥5.6 mmol/L (100 mg/dL) (If ≥5.6 mmol/L [or known T2DM] recommend an OGTT)	≥1,7 mmol/l	<1,03 mmol/l

>16	• Use existing IDF criteria for adults, ie:
	• Central obesity (defined as waist circumference ≥ 94cm for Europid men and ≥ 80cm for Europid women, with ethnicity specific values for other groups*)
	• plus any two of the following four factors:
	  • raised triglycerides: ≥ 1.7mmol/L
	  • reduced HDL-cholesterol:
	• Blood pressure Systolic ≥130/ diastolic ≥85 mm Hg
	• Glucose ≥5.6 mmol/L (100 mg/dL)				

Biomarkers of Atherosclerosis and CVD

CVD is the leading cause of death in western societies, and well-known risk factors like obesity and related comorbidities have been linked to atherosclerosis progression.

The atherosclerotic phase starts in infancy, but it progresses more quickly in children with obesity and other risk factors. Fatty streaks and fibrous plaques were related to previously measured BMI in pathology studies of children who died from other causes. Newer noninvasive techniques have recently revealed the precursors of CVD in children and adolescents, with endothelial dysfunction, a biomarker of arterial injury, being one of the first abnormalities discovered. The carotid artery's intima-media thickness (IMT) is a reliable tool for predicting CVD. Obese children with MS symptoms such as hypertension, dyslipidemia, or decreased glucose tolerance have been found to have higher IMT. With early vascular changes in obese children with MS, it appears that obesity-related cardiovascular risk factors such as hypertension, dyslipidemia, and insulin resistance, rather than obesity itself, are linked to elevated IMT. In fact, while obesity is an independent indicator of CVD in adults, there is insufficient evidence to relate obesity to CVD in children.

Other risk factors for CVD in children, such as left ventricular hypertrophy, elevated homocysteine, CRP, and lipoprotein concentrations, have been related to CVD in addition to the conventional risk biomarkers for CVD in children (glucose, insulin, and lipid profile concentrations). Central adiposity has higher levels of circulating high sensitivity (hs) CRP, which is consistent with the proinflammatory condition correlated with visceral adiposity. Furthermore, elevated hsCRP levels could play a role in the development of arterial thrombosis and endothelial injury repair.

New biomarkers linked to the atherosclerotic mechanism or associated decline in heart function have been studied in young people with obesity and MS. Troponin and B-type natriuretic peptide, for example, have historically been used to diagnose cardiac disorders such as acute coronary syndrome and myocardial infarction. In children and adolescents with MS, circulating high-sensitivity troponin T (hs-TnT), a sensitive biomarker of cardiac dysfunction, is higher than in obese children without MS and children with a typical BMI. Rather than childhood obesity, it is the unfavorable metabolic profile that is related to elevated hs-TnT concentrations. Adults with increased troponin concentrations had underlying CVD or a high-risk phenotype for CVD.

The Hs-TnT and N-terminal pro-brain natriuretic peptide (NT-proBNP) are direct markers of functional and structural injury of the cardiovascular system, as well as predictors of myocardial damage. Studies show that NT-proBNP concentrations are lower in obese males than in the normal BMI group and higher in obese hypertensive children than in obese normotensive children, suggesting that NT-proBNP may play a role in obesity-related hypertension. More, a favorable association was established between NT-proBNP and adiponectin concentrations only in female adolescents, this being greater in girls with a BMI-z-score>2.5, meaning that, while obesity does not specifically impact NT-proBNP concentrations in female adolescents, the magnitude of obesity influences the association between NT-proBNP and adiponectin.

Lipid profile. The lipid status of the 100 children examined expressed various deviations, so in 27% there are increased values of cholesterol, LDL values> 150 mg / dl, and HDL <35 mg / dl and 29% with values increased triglycerides> 150mg / dl.

Hepatic Insulin Resistance

The liver is the main goal of insulin action and it plays a significant role in substrate metabolism. Following a glucose load, insulin is released from the β cell and passes directly to the liver through the portal vein, where

it binds to the insulin receptor and triggers two primary gene transcription actions. Firstly, insulin causes FoxO1 to be phosphorylated, preventing it from accessing the nucleus and lowering the expression of gluconeogenic genes such as phosphoenolpyruvate carboxykinase and glucose 6-phosphatase. Hepatic glucose intake is reduced as a result. Secondly, insulin stimulates the transcription factor sterol regulatory element-binding protein (SREBP)-1c, which increases the transcription of genes involved in fatty acid and triglyceride (TG) biosynthesis, most notably ATP-citrate lyase, acetyl-coenzyme A carboxylase, and fatty acid synthase, all of which are involved in the *de novo* lipogenesis (DNL) process. DNL synthesizes TGs, which are packaged with apoliprotein B (apoB) into very low-density lipoproteins (VLDL) for storage or utilization through reciprocal activation of lipoprotein lipase (LPL) on the surfaces of endothelial cells in adipose or muscle tissues.

Insulin-resistant individuals usually have "selective" or "dissociated" hepatic insulin tolerance, suggesting they have impaired glucose homeostasis (mediated by the FoxO1 pathway) but elevated insulin-mediated hepatic DNL (mediated by the SREBP-1c pathway). Increases in hepatic glucose production, formation of proinflammatory cytokines, excess triglyceride release by the liver, low HDL cholesterol levels, and a rise in relatively cholesterol-depleted LDL particles occur when free fatty acid (FFA) flux is increased inside the liver, either by DNL or FFA distribution via the portal vein, impairing hepatic insulin action. Intrahepatic aggregation of FFA and lipid is harmful to liver insulin sensitivity since toxic lipid-derived metabolites such as diacylglycerol (DAG), fatty acyl CoA, and ceramides are generated. These contribute to the activation of protein kinase C-ε (PKC-ε) and the serine/threonine phosphorylation of IRS-1, which inhibits hepatic insulin signaling.

The augmented adipose tissue mass associated to obesity often leads to elevated lipolysis and FFA turnover. Insulin normally prevents adipose tissue lipolysis; but, in insulin-resistant individuals, the mechanism is prolonged, resulting in increased FFA release into the bloodstream. Furthermore, visceral adipocytes are more susceptible to catecholamine-stimulated lipolysis than subcutaneous adipocytes, raising FFA flux even more. Adipocyte hypertrophy and cytokine activation are also aided by macrophage infiltration into adipose tissue. Insulin action in other organs, such as the liver and muscle, is also detected by these circulating cytokines.

NAFLD is most often asymptomatic condition, is a risk factor in decompensation of liver function (high frequency of liver cirrhosis and liver carcinoma), worsening of cardiovascular disorders

In the total group of 100 examined children, in 34% of cases the presence of elevated ALT values ≥ 40 U / L was determined, and at USG an increase in liver size by 7-10%, correlating with increased BMI ≥ 28 kg / m² .

Muscle Insulin Resistance

Increased plasma FFA levels interrupt the glucose-fatty acid cycle and insulin-mediated glucose transfer in skeletal muscle downstream of an insulin-resistant liver, simplifying hyperglycemia development. The deposition of intramyocellular lipid in skeletal muscle can also play a direct role in the pathogenesis of insulin resistance and metabolic syndrome by activation of PKC-ε and ensuing impairment of insulin signaling.

Lipid Partitioning

The distribution of body fat in different organs and compartments is referred to as lipid partitioning. While the bulk of excess fat is contained in the subcutaneous depot, there are other storage options, such as the intra-abdominal (visceral) fat compartment and insulin-responsive tissues like muscle and liver.

The "portal-visceral" model is one theory for explaining the connection between obesity and insulin resistance. According to this theory, increased adiposity leads to fat accumulation in the visceral depot, which results in increased portal and systemic free fatty acid (FFA) flux. Most age ranges and ethnicities have shown links between visceral adiposity, insulin resistance, and comorbidities.

Insulin resistance is closely linked to subcutaneous fat, which does not drain into the portal system, in both stable obese and diabetic men. Similarly, truncal subcutaneous fat mass has been shown to predict insulin resistance in obese women independently. Visceral and subcutaneous fat have different biologic reactions, with visceral fat being more resistant to insulin and having higher catecholamine sensitivity. Visceral and subcutaneous abdominal fat, probably by various pathways, can lead to insulin resistance. Research in obese adolescents has shown that the ratio of visceral to subcutaneous fat could be the determinant of their metabolic effects rather than their total quantity. Indeed, obese teenagers with a high ratio show a distinctly adverse metabolic profile with severe insulin resistance and changes in glucose and lipid metabolism, while not actually being more obese than others. Furthermore, besides being closely linked to elevated levels of visceral fat, intrahepatic fat is linked to insulin resistance in obese youth, regardless of all other fat depots.

The "ectopic lipid deposition" hypothesis is an alternative theory for explaining the connection between obesity and insulin resistance. This hypothesis is based on the findings of elevated lipid content in liver or muscle in obesity and in T2DM, being a predictor of insulin resistance. Furthermore, due to a shortage of subcutaneous fat tissue in conditions like lipodystrophies, all fat is retained in the liver and muscle, resulting in severe insulin resistance and diabetes. Muscle attenuation on CT is a greater predictor of insulin resistance in obese adults (BMI > 30) compared to visceral fat. Increased IMCL content was shown to be a good determinant of insulin resistance in adults and obese teenagers in studies conducted *in vivo* using

'H-NMR spectroscopy. In comparison to visceral fat, lipid deposition in hepatocytes to generate intrahepatocellular lipid (IHCL) is a good predictor of insulin resistance. Obesity-related morbidity can begin when subcutaneous fat exceeds its potential for storing excess fat and starts to shunt lipid to ectopic tissues, such as liver and muscle, resulting in peripheral insulin resistance.

A decrease in fat β oxidation, linked to low aerobic capacity, a reduced number or dysfunction of mitochondria, or reduced SNS tone, is another proposed cause of IMCL and IHCL accumulation. The outcome of IMCL or IHCL accumulation on peripheral sensitivity is thought to be due to a change in the insulin signaling pathway in muscle, which is caused by fat derivatives such as long chain fatty acyl-CoA and diacylglycerol within the hepatocyte or myocyte. The derivatives set off the serine/threonine kinase cascade, allowing serine phosphorylation of IRS-1 that inhibits insulin signaling. In the liver, lipid accumulation, especially diacylglycerol, triggers the inflammatory cascade by inducing c-Jun N-terminal kinase (J NK-1).

Conclusion.

In this preliminary study we have found that in the cohort of obese Moldovan children among the most common complications of obesity constantly elevated blood pressure, impaired lipid status, the presence of sleep apnea syndrome, they are associated with increased HOMA-IR indices ≥3 and BMI ≥ 28 kg / m. Obese children have high metabolic risk and demand for a therapeutic approach and intervention as early as possible, to prevent the installation of irreversible complications in adulthood. Evidence shows that a combination of dietary interventions, behavioral therapy, and exercise is a significant impact in reducing the number of children with metabolic syndrome.

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