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RESEARCH ARTICLE

CHANGES IN LIPID PROFILE AND LIPOTOXICITY IN PEOPLE WITH HYPOTALAMIC (MORBID) OBESITY

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Abstract

Accumulation of visceral fat causes a lipotoxic effect on the hypothalamus. Hypothalamic inflammation closes a vicious circle, aggravating the disturbance of neuroendocrine mechanisms to regulate metabolic balance, including coordination of energy consumption (during basic metabolism, physical activity, thermogenesis) and proper feeding behavior, the study group included 62 individuals (women) with obesity. Each patient met the diagnostic criteria for idiopathic hypothalamic syndrome – the neuroendocrine form with obesity.The current study shows that obesity of hypothalamic origin is associated with a dyslipidemia that progresses simultaneously with the increase of the body mass index.

Introduction:-

Inflammation of the hypothalamus is one of the basic mechanisms of disorders of the normal physiological regulation of homeostatic energy and plastic balance. Namely, discordances in this way lead to the genesis of metabolic syndrome, obesity and type 2 diabetes [1].

A diet with a high carbohydrate and fat index is most likely the main behavioral and ecological factor, which makes a significant contribution to the development of inflammatory processes in the hypothalamus and the development of severe consequences for energy and plastic metabolism [2, 3, 4].

The bidirectional interdependence of brain function and metabolism is evidenced by the fact that discrete neural networks in the hypothalamus have the ability to detect fluctuations in the concentration of long-chain fatty acids in the bloodstream, sensitive to changes in carbohydrates, lipid and protein metabolism, thus ensuring regulation of nutritional behavior, food and water consumption [5, 6].

Defects of the neuronal response to negative feedback signals from obesity in the circulatory bed (leptin, insulin), leptin resistance and insulin resistance aggravate the inflammatory responses of cells, precisely because of excess visceral fat [7, 8, 9, 10].

A dangerous consequence of excess tissue lipids that are not suitable for their storage is lipotoxicity. Accumulation of visceral fat causes a lipotoxic effect on the hypothalamus, whose inflammation closes a vicious circle, aggravating the disturbance of neuroendocrine mechanisms to regulate metabolic balance, including coordination of

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energy consumption (during basic metabolism, physical activity, thermogenesis) and proper feeding behavior, as well as control of reproduction and growth [11, 12, 13].

With obesity, the hypothalamus becomes insensitive to leptin and insulin, which indicates a deterioration of the regulation of the energy balance by the hypothalamus. Accumulation of ectopic lipids in peripheral tissues, such as β cells of the pancreas, liver, heart, and skeletal muscle, continues to increase the lipotoxic impact associated with insulin resistance, type 2 diabetes, hepatic steatosis, atherosclerosis, and heart failure [15].

The aim of the research consists of determining the dynamism of changes in lipid and atherogenic metabolism in obese people of hypothalamic origin. Objectives: to evaluate the type of adiposity and body mass, to estimate the plasma concentration of lipoproteins; to determine the atherogenic coefficient; perform a comparative analysis between the levels of plasma lipoprotein concentration and the atherogenic coefficient according to the severity of adiposity, to determine the evolution of dyslipidemia and atherogenicity in patients with hypothalamic obesity.

Observation:-

The study group included 62 individuals (women) with obesity, the age limits varying between 18-53 years, with an average of 36.3 ± 3.4 years. Each patient met the diagnostic criteria for idiopathic hypothalamic syndrome – the neuroendocrine form with obesity. Adiposity in these patients is present from childhood or appeared until the age of 30 years and is associated with other neuroendocrine and thermoregulatory disorders, as well as with psychological, vegetative disorders due to the absence of organic brain or somatic lesions, which could develop obesity.

Therefore, people with a history of organic brain or somatic lesions with signs of obesity and overweight were excluded from the study. Each patient included in the research list had abdominal obesity determined by the ratio between waist-to-hip ratio (WHR) and increased body weight, determined by body mass index (BMI). As is well known, abdominal obesity, characterized by increased adipose tissue surrounding the intra-abdominal organs, is also called visceral or central obesity (VO). The assessment of WHR and BMI values was performed according to the recommendations of WHO experts [WHO. Physical Status: The Use and Interpretation of Anthropometry: Report of a World Health Organization (WHO) Expert Committee. Geneva, Switzerland: World Health Organization; 1995]. The BMI value ≥ 30 kg / m^2 determined the obesity, and the value of the WHR ratio ≥ 0.88 determined the visceral type of obesity.

Of all the patients examined, with a pathological history, some people also had a diagnosis of type 2 diabetes (diabetes mellitus, T2D). These subjects were included and analyzed in a separate group. Thus, according to clinical data and the results of anthropometric measurements, patients were divided into two groups: patients with VO without T2D (n = 46), age limit: 18-46 years, mean age: 34 ± 3 years and patients with VO + T2D (n = 16), age limit: 46-54 years, mean age: 48.3 ± 3.5 years. The duration of the disease from the establishment of the diagnosis is between 2-8 years, average: 4.7 ± 0.4 years. The control group included 15 normal-weight women, practically healthy; age limits: 20-47 years, average age: 34.2 ± 3.1 years.

Plasma concentrations of triglycerides (TG) and total cholesterol (TC) were determined by the enzymatic method in the automatic analyzer (Analyzer A15, BioSystem S.A., Spain). High-density lipoprotein cholesterol (HDL-C) was dosed into the supernatant after serum precipitation of low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) with bivalent cations. LDL-C and VLDL-C values were calculated according to the Friedewald formula: LDL-C = TC - (TG / 5) - HDL-C (mg / dL). VLDL-C = TG / 5 (mg / dL). We can alternatively use units: mmol / L. The atherogenic coefficient (AC) was also established by calculation: AC = (TC - HDL-C) / HDL-C.

Dyslipidemia was determined at TG values > 1.8 (mmol / L) and / or TC > 6.2 (mmol / L), HDL-C < 1.0 (mmol / L). Blood was collected from each person on an empty stomach in the morning.Theveracity of the statistical data obtained was estimated with the application of the t-Student criterion. As a criterion of statistically true significance, the level of significance lower than 0.05 ($P < 0.05$) was considered.

The mean values of the WHR index in all patients were higher compared to the values in the control group. For those with VO without T2D, the mean WHR value was 1.28 ± 0.07; in patients with VO + T2D: 1.35 ± 0.08; and for the persons of the control group only: 0.74 ± 0.04. The average values of the WHR indices in patients with VO

without T2D (*** – P < 0.001) and in those with VO + T2D (*** – P < 0.001) of the value average of the WHR index of the persons of the control group.

The BMI value in patients with VO without T2D was 38.8 ± 2.7; and in the case of VO + T2D: 45.8 ± 3.1; but in the persons of the control group only: 22.3 ± 1.3. It is obvious that a statistically authentic distinction was registered between the BMI values in patients with VO without T2D (P < 0.001), and in patients with VO + T2D (P < 0.001) compared to the subjects of the control group. These data demonstrate that the subjects in the study group and especially in the cases with VO + T2D had abdominal adiposity, ie visceral, against the background of significantly increased body weight compared to normal weight people. The data of the lipid metabolism examination are presented in Table 1.

The values of the lipid profile indices in patients were modified and authentically differed from those of the control group. Hypertriglyceridemia and hypercholesterolemia characterized by elevated total cholesterol and decreased HDL-C with an increase in LDL-C, VLDL-C lipoprotein fractions of AC were revealed. Lipid profile values are altered in all patients depending on the severity of obesity. A statistically significant distinction was recorded between the values of the lipid profile indices and those of the subjects in the control group: TG in patients with VO Class II and VO Class III (P < 0.001); TC in patients with VO Class II (P < 0.05), VO Class III (P < 0.01); HDL-C in patients with VO Class I (P < 0.05); LDL-C in patients with VO Class I (P < 0.05) and VO Class III (P < 0.001); VLDL-C in all groups of patients with VO (P < 0.001).Atherogenic coefficient (AC) in patients with VO Class I, Class II and Class III (P < 0.01) (Picture 2).

Discussion:-

These data demonstrate that patients with VO without T2D and especially those with VO + T2D had mixed dyslipidemia and had a high atherogenic risk. The analysis of the lipid profile data according to the severity of obesity are presented in Picture 1. In association with the severity of obesity, the severity of dyslipidemia increases, as well as the risk of genesis of atherogenicity.

The current study shows that obesity of hypothalamic origin is associated with a dyslipidemia that progresses simultaneously with the increase of the body mass index. This is explained by the intervention of several neuroendocrine regulatory mechanisms. It is now well known that visceral obesity expresses a lipotoxic impact is accompanied by decreased tissue insulin sensitivity [10].

The evolving increase in body weight designates all patients as insulin resistant with hyperinsulinism. The mechanism by which hyperinsulinism can induce lipid changes is complex. It includes not only an increased hepatic production of triglycerides, but also a decrease in their circulation. Hypertriglyceridemia can also be explained by the plasma transfer of increased amounts of triglycerides from fat stores in adipose tissue [6]. Elevated total cholesterol can be explained by increased levels of LDL-C fractions, because the serum quantity of HDL-C is low. This is the opinion of other authors [7, 8, 9].

The decrease in HDL-C is due to the reduced synthesis and secretion in the liver caused by insulin resistance. The decrease in the serum concentration of HDL-C is also due to the decrease in the rate of metabolism of VLDL-C, because these lipoproteins have their origin in this process as well. Elevated plasma LDL-C levels are attributed to decreased liver degradation, as well as insulin resistance and hyperinsulinemia. The increase in VLDL-C is also due to increased liver generation, it is supported by the abundant flow of free fatty acids from adipose tissue, because of peripheral insulin resistance [2]. It has been found that insulin-sensitive lipoprotein lipase activity in insulin-resistant patients is substantially reduced [3].

The authors assume that this decrease is due to the inability of circulating insulin to stimulate the transcription of the lipoprotein lipase gene into adipocytes.Thus, we can conclude thatoverweight in all cases is accompanied by dyslipidemia. It is more pronounced in middle-aged people. Lipid disturbances in subjects with adiposity develop through several endogenous mechanisms not yet elucidated to the end.

Conclusion:-

Obesity can be caused by pathology of the central nervous system and is accompanied by many associated diseases. which will subsequently decrease the hypothalamic production of neuropeptide Y.Adipose tissue is not only a

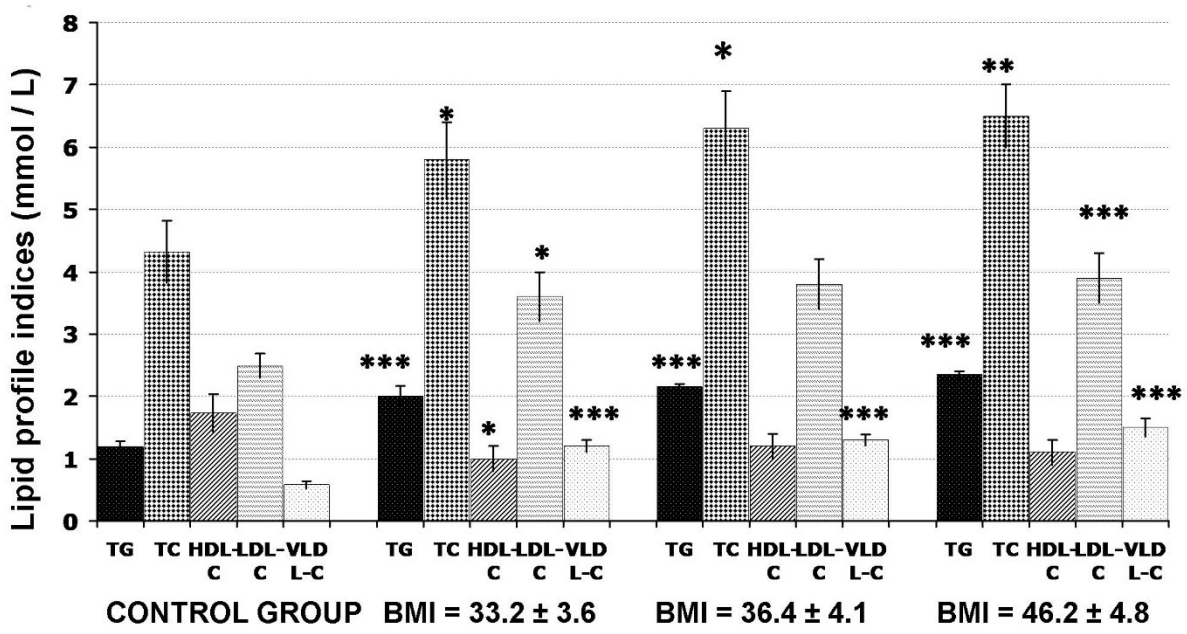
deposit of energy that secretes fatty acids to provide fuel to the body, but also an endocrine organ producing high protein substances with important physiological functions.

These factors participate in autocrine and paracrine regulation within adipose tissue and can substantially influence the functions of other organs, such as skeletal muscle, pancreas, liver.The function of adipose tissue, as an endocrine organ, is important to understand the relationship and interrelationship between excess fat and pathological conditions, such as insulin resistance and type 2 diabetes, cardiovascular disease, obstructive sleep apnea and other types of nocturnal hypoventilation, type 2 diabetes, dyslipidemia, hypertension and thromboembolic disease.

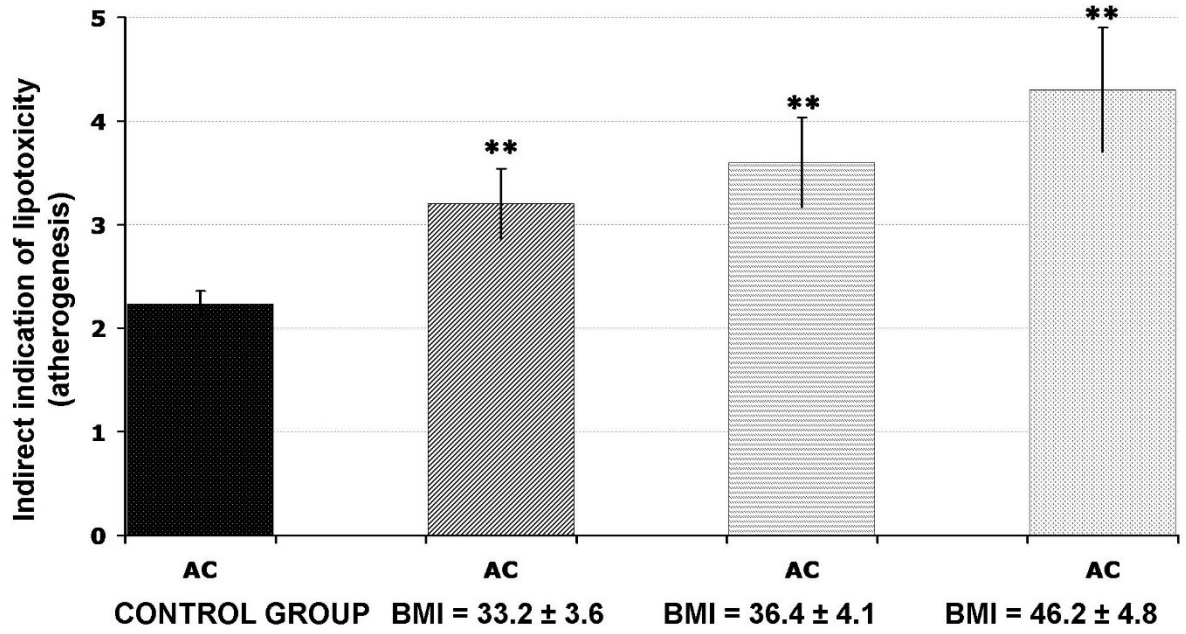
Table 1:- Indices of the lipid profile of the subjects in the study groups.

Indices	The control group (normal weight) (n = 15)		VO without T2D (n = 46)		VO + T2D (n = 16)	
	Limits	M±m	Limits	M±m	Limits	M±m
TG (mmol/L)	0.98-1.76	1.19±0.05	1.92-2.47	2.13±0.18**	1.96-2.64	2.33±0.21***
TC (mmol/L)	3.34-5.12	4.32±0.5	5.88-6.86	6.26±0.6*	5.92-6.94	6.41±0.5**
HDL-C (mmol/L)	1.14-2.26	1.73±0.3	1.05-1.82	1.44±0.2	0.96-1.72	1.35±0.2
LDL-C (mmol/L)	1.97-2.96	2.49±0.2	3.12-4.47	3.68±0.4**	3.27-4.58	3.77±0.4**
VLDL-C (mmol/L)	0.29-0.98	0.58±0.06	0.53-1.46	0.95±0.08***	0.97-1.76	1.22±0.13***
AC	1.98-2.77	2.23±0.13	2.32-3.87	3.36±0.3**	3.79-4.67	4.13±0.5**

Note: * – P < 0.050; ** – P < 0.010; *** – P< 0.001.
P – the level of significance of the difference between the indices of patients with VO without T2D and those with VO + T2D compared to the control group.



Picture1:- Lipid profile indices by severity of visceral obesity (VO)**Note: * – P < 0.050; ** – P < 0.010; *** – P < 0.001.**



Picture 2:- Indirect indication of lipotoxicity reflecting the risk of atherogenesis expressed by the atherogenic coefficient (AC). Note: * – P < 0.050; ** – P < 0.010; *** – P < 0.001.

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