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Metabolic phenotyping: is it so important?

Prybyla O

Institute of Endocrinology and Metabolism of the National Academy of Medical Science", Kyiv, Ukraine

Type 2 diabetes is one of the most pressing problems not only for endocrinologists and their patients, but also for the whole society. The relationship between the stage of obesity, the risk of cardiovascular diseases and mortality from them has been established.

Throughout our life we realize natural instincts - food, reproduction, self-preservation. All factors that influence them can cause pathological changes in carbohydrate and lipid metabolism. Those features are mainly determined by phenotypic characters. The negative consequences of the established phenotype are manifested in elderly and old age. This is the time when the embodiment of the basic natural instincts is completed, and the adaptive - compensatory processes are inhibited.

Metabolic disorders, as for example T2DM, are based on metabolic syndrome in the presence of permissive conditions, include impaired carbohydrate tolerance, dyslipidemia, decreased overall metabolism, hyperproduction of uric acid and others. Hormonal imbalance includes inadequate secretion and peripheral reception of insulin, steroid hormones (sex steroids and their precursors, as well as corticosteroids), incretins, changes in the concentration of biologically active regulatory molecules (cytokines, growth factors, leptin, adiponectin, tumor necrosis factor 1)

The criteria of metabolic syndrome (MS) have been repeatedly revised, the list and threshold values of the main anthropometric, clinical, laboratory indicators have changed. However, the principle of clustering several disorders as risk factors for the development of "dysmetabolic" diseases - T2DM, gout, dyslipidemia, cardiovascular diseases etc. is unchanged.

In our opinion, such "instability" in the definition of metabolic syndrome is associated with the heterogeneity of phenotypes in different populations, because the individual manifestations of main signs of this complex may depend on genetic, constitutional, psychosocial characteristics, lifestyle, and others.

The metabolic phenotype plays an important role in the development of cardiovascular catastrophes and metabolic disorders, such as T2DM, hypertension, atherosclerosis, and coronary artery disease. Due to the concept developed by the Department of Clinical Pharmacology of the State Institution "V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine" , the metabolic phenotype consists of three different phenotypes that have different mechanisms of formation and manifestation. The development of each phenotype occurs in violation of various types of hormonal-metabolic mechanisms. The formation of an alimentary phenotype occurs when there is an imbalance between the intake and the expenditure of energy. It is based on the characteristics of lipid and carbohydrate metabolism. The social phenotype is formed due to the realization of the instincts of self-preservation and self-realization. The hormonal-metabolic provision of both processes is predetermined by the action of glucocorticosteroids (in particular, cortisol). The abdominal-visceral phenotype is based on the characteristics of sexual activity due to the redistribution of sex steroids and dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-s), which occur in elderly age.

It is also important to note that according to the definition obesity, it is diagnosed using the waist circumference, and not the body mass index. It is known that the waist circumference correlates with the levels of visceral obesity and insulin resistance. Clinical observations have shown that these indicators positively correlate with the risk of cardiometabolic diseases at the total population level. However, at an individual level, the distribution of fat in the body and impaired function of adipose tissue better predicts the insulin resistance and related complications than the total fat mass.

Adipose tissue dysfunction manifests by itself due to changes in the topography of adipose tissue, adipocyte hypertrophy, impaired lipid metabolism and local inflammation. The adipose tissue oxygenation may be a key factor in these processes.

Thus, different clinical observations indicate that abdominal obesity (an excess of visceral adipose tissue in the body) has the worse prognosis of the development of metabolic syndrome, type 2 diabetes and cardiovascular disease and mortality than subcutaneous fat accumulation. An excess of visceral fat can develop as the specific hormonal-metabolic profile associated with changes in sex steroid levels against the background of general obesity, or in thin people with an imbalance of stress / anti-stress, anabolic / catabolic hormones. This also confirms the theory of metabolic phenotype.

Recently, a new approach - calculation of the Visceral Adiposity Index - has been used to determine the morphology of abdominal adipose tissue and its dysfunction.

This empirical, gender-specific model is based on anthropometric measurements (body mass index, waist circumference) and metabolic parameters (triglycerides, high density lipoprotein levels), and considers the location and functional features of adipose tissue.

Clinical studies have shown that the Visceral Adiposity Index, instead of previous surrogate markers, better correlates with the degree of insulin resistance, cardiometabolic risk and type 2 diabetes mellitus. This model can be used as a predictor and clinical indicator of the presence of insulin resistance / hyperinsulinemia (according to the euglycemic hyperinsulinemic Clamp), a violation of the distribution and function of adipose tissue and metabolic syndrome`s disorders.

This work is partly presented at Joint Event 18th International Conference on Metabolomics and Proteomics at October 21-22, 2020 in Frankfurt, Germany

These results were obtained by examining various patient populations, including DM2 patients, and became the basis of the hypothesis that VAI can be considered a marker of adipose tissue dysfunction and an indirect reflection of the degree of cardiometabolic risk.

Recent clinical studies suggest that detailed metabolic phenotyping of obese people can be a useful tool for revealing the pathophysiology of metabolic disorders, identifying individuals or high-risk subgroups, and identifying ways to optimize prevention and treatment strategies for cardiometabolic diseases.

Currently, it is proved that the presence of general obesity in most cases is an independent risk factor for dysmetabolic conditions. However, large number of clinical studies had revealed several additional MS phenotypes that differ in the degree of metabolic disturbances and the ratio of subcutaneous and visceral adipose tissue.

During the last years, the classification of pathophysiological phenotypes of the metabolic syndrome is increasingly used. It combines internal and external signs: biochemical parameters (characteristics of glucose, lipid metabolism, sensitivity to insulin), the ratio of subcutaneous and abdominal fat, blood pressure The main phenotypes that reflect possible combinations of the metabolic profile and degree of obesity are the following: metabolically healthy obesity, metabolically healthy with normal weight , metabolically unhealthy obesity, metabolically unhealthy with normal weight .

The group of “metabolically unhealthy with normal weight” (MUNW) has the interest. Its formation became the basis of the concept of "obesity paradox."

In the last decade, many studies have shown that overweight people (BMI 25-29.9 kg / m2), patient with moderate obesity (BMI 30-34.9 kg / m2) have a longer life expectancy, a better cardiovascular prognosis than patients with BMI up to 25 kg / m2.

It is known that people with normal body weight may have a metabolically unhealthy phenotype, which is a special cluster of MS, accompanied by increased metabolic risks: the development of diabetes mellitus, disorders of the excretory, nervous, musculoskeletal systems, cardiometabolic.

During the evaluation of the results of the Framingham study, according to a survey of 2902 people, a cohort of patients with normal body weight (BMI up to 25 kg / m2), but with a high metabolic and cardiac risk was described.

This group, in contrast to healthy lean people, had typical signs of obesity: metabolic hyperinsulinemia, primary insulin resistance, hypertriglyceridemia, higher blood levels of leptin, TNF-a and lower levels of adiponectin. Also noteworthy are the signs of adipogenesis disorders, an increase in body fat (due to both visceral and subcutaneous depot), even with normal BMI, and a decrease in energy expenditure associated with physical activity.

There is a high heterogeneity in the prevalence of MUNW phenotype: from 5% to 45%, which may be due to differences in sample size, differences in the definition of MUNW and normal weight, social and demographic factors. People with MSDs are often characterized by excess visceral adipose tissue and ectopic fat deposition, inflammation of adipose tissue, decreased skeletal muscle mass, and low cardiorespiratory efficiency. However, individuals from the group MUNW were slightly "fatter" than in the control group of metabolically healthy study participants, which alone may be the cause of some differences. Additional research is needed to better understand the characteristics of the MUNW phenotype, the causes of metabolic dysfunction in the absence of obesity, and to evaluate potential treatments to develop clinical guidelines.

As part of the European Prospective Investigation into Cancer and Nutrition Potsdam study, a cohort study was conducted that included 2,027 participants, including 706 cases of diabetes. It was noted that individuals with the phenotype had a larger waist circumference than women (women: 75.5 vs. 73.1 cm; men: 88.0 vs. 85.1 cm), higher levels of HbA1c (6, 1 % vs. 5.3%), triglycerides (1.47 vs. 1.11 mmol / L), highly sensitive C-reactive protein (0.81 vs. 0.51 mg / L), lowering HDL cholesterol (1.28 vs. 1 , 49 mmol / l) and adiponectin (6.32 vs. 8.25 μg / ml). The development of diabetes mellitus in MUNW was associated with risk factors such as smoking, hypertension and less physical activity compared with the control group. The risk of diabetes was almost the same in the group of participants with normal weight and in the groups with overweight and obesity.

Aim.

All described data was the start point of the study of Department of Age Pathology and Clinical Pharmacology of the State Institution “V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Medical Sciences of Ukraine” .The aim of the work is to describe the types of the body composition and metabolic characteristics of patients with type 2 diabetes, depending on obesity levels.

Methods and objectives.

The first step in this study was the analysis of metabolic parameters in different groups of patients with type 2 diabetes. 51 patients with type 2 diabetes were examined, aged 30 to 81 years, without and with obesity. Duration of DM2 was from 1 till 20 years.

Anthropometric parameters (height, body weight, BMI, waist and hips, thickness of fat folds; body composition parameters (bioelectrical impedance method)), metabolic parameters: glucose metabolism (fasting blood glucose, HbA1c, insulin and C-peptide levels), lipids, uric acid were determined. The indices of atherogenicity (IA), central obesity (COI) and visceral obesity (VAI) were calculated using known formulas for men and women. Statistic analysis was provided with MedStat v.5.2.

Results.

All patients were divided into 2 BMI groups: 1) obese subjects (n = 17, BMI <30 kg / m2); 2) patients with obesity (n = 34, BMI ≥30 kg / m2) who practically did not differ in age, HbA1c level, fasting glycemia, uricemia, uricosuria, muscle mass on the body and extremities, total bone mass, levels ,T.cholesterol, TG, HDL, COI, VAI (P> 0.05). Patients without obesity have significantly higher percentages of water into the body, estimated metabolic age (P <0.05).

According to our additional studies, the minimum levels of visceral fat in both groups did not differ statistically (7- in the group without obesity, and 7.5 - with obesity), in contrast to the maximum (19 and 26.5, respectively) (P <0, 05)

Discussion and conclusion.

As a result of comparative analysis, it was found that patients with obesity had higher values of waist and thing level, thickness of fat folds, percentage of total body fat, visceral fat, increase of fat levels in the body and both extremities, atherogenic index (P <0.001) . Based on our data, we recommend the use of indicators in medical practice: visceral fat levels, estimated metabolic age,% of total fat, or visceral obesity index, which better identify possible cardiometabolic risks in patients with metabolically unhealthy normal weight and metabolically unhealthy obesity in Ukraine.

The data obtained are the basis for further selection of markers of hormonal and metabolic changes in persons with appropriate phenotypic characteristics and development of personalized recommendations for their correction.

Therefore, the next stage of our work is the study of changes in the levels of the stress hormone cortisol, its functional antagonist DHEA-C and indicators of carbohydrate and lipid metabolism depending on the degree of obesity and the type of distribution of fat (gynoid, android) at different stages of development of type 2 diabetes.

We believe that our overall results will allow us to differentiate even more depending on a specific metabolic phenotype and to personify approaches to the diagnosis and treatment of both metabolic syndrome and type 2 diabetes mellitus and its complications.

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