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Review

The role of metabolic syndrome variant in the malignant tumors progression

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ABSTRACT

Metabolic syndrome (MS) is one of the leading risk factors for the development of some common cancers (endometrial cancer, postmenopausal breast cancer, colorectal cancer). Currently, a drug-induced metabolic syndrome related with androgen deprivation therapy in patients with prostate cancer represents a serious medical problem. Not only MS, or its individual components, but MS variants with different levels of leptin, adiponectin, visfatin, resistin are associated with tumor invasion, metastasis and survival rates in patients with MS-associated malignancies.

Contents

Abbreviations: MS, metabolic syndrome; IDF, International Diabetes Federation; ESH-ESC, The European Society of Cardiology and the European Society for Hypertension; IL-6, IL-10, IL-18, interleukins 6, 10 and 18; LDL, low-density lipoproteins; HDL, high density lipoproteins; AR, androgen receptors; ERα, estrogens receptors alpha; PPARs, peroxisome proliferator-activated receptors; CRPC, castration-resistant prostate cancer; MRI, magnetic resonance imaging.

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1. Metabolic syndrome as a risk factor for the development of malignant tumors

Metabolic syndrome (MS) is one of the leading risk factors for the development of cardiovascular diseases, type II diabetes mellitus, pathology of the reproductive system and of some common cancers (endometrial cancer, postmenopausal breast cancer, colorectal cancer) [1]. The International Diabetes

Federation (IDF, 2005) defined common criteria for diagnosing MS. In accordance with IDF guidelines, diagnosis of MS requires the necessary presence of abdominal type of obesity (waist circumference greater than 94 cm for Caucasian men and 80 cm for Caucasian women) combined with at least two of the four additional criteria: increase in blood serum triglyceride level of more than 1.7 mmol/l or previously treated dyslipidemia; decrease in high-density lipoproteins (HDL) cholesterol (less than 1.03 mmol/L for men and 1.29 mmol/L for women); high blood pressure (systolic over 130 mm. Hg, or diastolic more than 85 mm. Hg, or antihypertensive therapy in history); increase in fasting blood glucose of more than 5.6 mmol/L, or previously diagnosed type II diabetes mellitus [2,3].

Besides the main diagnostic criteria, the IDF consensus group recommends to study a additional metabolic criteria for research purposes. Additional metabolic criteria for research are: evaluation of fat distribution disorders (total fat distribution, central fat distribution, adipose tissue biomarkers: leptin, adiponectin, fat content in the liver); atherogenic dyslipidemia (apoprotein B, small particles of low-density lipoproteins (LDL), dysglycemia; insulin resistance (insulin fasting level, insulin resistance index, insulin resistance according to the minimal Bergman model); pro-inflammatory status (elevated level of C-reactive protein, increased levels of inflammatory cytokines - tumor necrosis factor, interleukin-6); prothrombotic status and hypercoagulable states markers (fibrinolytic factors, tissue activator of plasminogen, fibrinogen, etc.). The study of these factors allows us to modify the diagnostic criteria for MS and also provide additional clinical data for MS ethnic-specific criteria formation [3,4].

Not only cardiovascular risk factors related to MS are frequently discussed in the literature but it has been also shown that MS is associated with increased risk of common cancers [5]. In a meta-analysis, Esposito K. et al. [5] showed that MS for women was associated with certain types of cancer (endometrial cancer, postmenopausal breast cancer, colorectal cancer). But for men, statistically significant associations between MS and liver cancer, colorectal cancer, and bladder cancer were identified. The relationship between MS and biliary tract cancers was found predominantly in Asian populations [5–11].

2. Panel of metabolic syndrome biomarkers: goals and opportunities

For many pathological conditions, medicine relies on biomarkers (proteins, metabolites, DNA and RNA markers) to assist in diagnosis and treatment when clinical signs are absent or not obvious [12]. In relation to such a common condition as MS, not only the panel of biomarkers recommended by IDF is used, but also various other panels in accordance with the goals and objectives set (Table 1).

3. Pathogenetic variants of metabolic syndrome: clinical and hormonal aspects

In accordance with the definition of International Diabetes Federation (IDF, 2005) and the European Society of Cardiology and the European Society for Hypertension (ESH-ESH) (2007), metabolic syndrome (MS) is a cluster of at least three of the five following components: abdominal obesity, high blood pressure, high blood sugar, high serum triglycerides and low high-density lipoprotein (HDL) levels. The proportion of patients with three MS components is significantly higher than that with four or five MS components [10,11,17,18]. The most common MS components were abdominal obesity, arterial hypertension and reduced HDL cholesterol level. In people residing in St. Petersburg and ranging in age from 30 to 55 years, the incidence of MS with all 5 components was 12.3% and 11.2% by IDF and ESH-ESC-definitions, respectively [18]. In the study of A.C. Santos et al. (2007), arterial hypertension was also the most frequent component of MS (IDF, 2005), however, carbohydrate metabolism disorders were observed more frequently (37.2%) than reduced HDL cholesterol level (30.4%) and increased blood serum triglyceride level (29.8%) [19]. According to data obtained from the study of Konradi A.O. (2011), the incidence of carbohydrate metabolism disorders in individuals with abdominal obesity was 39.1%. These results were consistent with the study of A.C. Santos [18].

There are no studies with strong recommendations for the identification of pathogentic variants of MS, however, the multicomponent nature of MS indicates that these variants evidently exist. Multivariate regression analysis showed that the high level of resistin, a hormone secreted by adipose tissue, was associated with peripheral artery disease in patients with arterial hypertension [20]. A small number of studies reported about adipokines and hormones associated with MS and obesity in patients with colorectal cancer. However, according to these studies and own published data, there are certain features of MS in these patients. The combination of abdominal obesity (29.4 ± 1.08 BMI), dyslipidemia and hypertension was often revealed, however, type II diabetes mellitus was rarely diagnosed in these patients. Patients with colorectal cancer can be divided into 2 subgroups: with normal and low level of adiponectin [21,22]. Nakajima T.E. et al. [23] reported that the serum levels of adipokines- resistin and visfatin were increased in colorectal cancer patients with MS compared to the control group patients (obese patients without colorectal cancer). According to the Japanese Classification of Colorectal Carcinomas, the levels of both hormones correlated with the disease stage and increased with disease progression [23]. However, since the TNM classification and the Japanese Classification of Colorectal Carcinomas do not fully correspond, it remains unclear whether such findings will persist. In addition, visfatin, a newly discovered adipocyte hormone, was found to influence the prognosis of endometrial cancer associated with obesity and MS. Endometrial cancer patients had significantly higher visfatin levels

Table 1
Panel of metabolic syndrome biomarkers depending on the purpose of the study.

Purpose of biomarkers determination	Panel biomarkers	References
Diagnosis of MS	The study of additional biomarkers is not recommended	[1,12]
Prevention of type II diabetes mellitus and MS	α-tocopherol, bradykinin, glucose, mannose, α-hydroxybutyrate	[13]
Identification of pathogenetic variants of MS for early detection, personalization of therapy and risk stratification	IL-6, IL-10, IL-18, TNFα, OxLDL, uric acid, leptin, adiponectin, ghrelin, PAI-1, paroxonase-1 Bio-Plex Pro Diabetes Assays panels (Bio-Rad)	[12,14] http://www.bio-rad.com/ru-ru/category/bio-plex-multiplex-immunoassay-system
	Various panels of interleukins, panels for hypercoagulable states	[15,16]

Note: MS - metabolic syndrome, IL-6, IL-10, IL-18 - interleukins 6, 10 and 18; TNFα - tumor necrosis factor alpha, OxLDL - oxidized low density lipoproteins; PAI-1 is an inhibitor of plasminogen activator 1.

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