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AN OVERVIEW OF METABOLIC SYNDROME IN OSSABAW MINIATURE PIGS

SINTEZĂ ȘTIINȚIFICĂ ASUPRA SINDROMULUI METABOLIC AL PORCILOR MINIATURALI OSSABAW

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ABSTRACT | REZUMAT

This paper highlights the current literature devoted to metabolic syndrome in Ossabaw miniature pigs. Metabolic syndrome is a group of risk factors such as central (intra-abdominal) obesity, insulin resistance, impaired glucose tolerance and hypertension. The aim of this paper is to emphasize the consequences of this pathology in Ossabaw miniature pigs. Consumption of excess kcal causes animals of the "thrifty genotype" such as Ossabaw miniature pigs to manifest components of the metabolic syndrome. This syndrome has a major impact on multiple organs. The main systems affected by obesity and metabolic syndrome in Ossabaw miniature pigs are the circulatory system, digestive system, particularly pancreas and liver, reproductive system and locomotor system.

Keywords: Ossabaw miniature pig, metabolic syndrome, obesity

Articolul urmărește evidențierea aspectelor întâlnite în literature curentă a sindromului metabolic al porcilor miniaturali Ossabaw. Acest sindrom cuprinde un grup de factori de risc precum obezitatea, rezistența la insulină, toleranță scăzută la glucoză și hipertensiune arterială. Obiectivul lucrării este de a sublinia consecințele acestei patologii asupra porcilor Ossabaw. Consumul în exces al kcal conduce, în cazul animalelor cu "genotip economic" precum porcii Ossabaw, la manifestarea sindromului metabolic. Acesta are un impact major asupra organismului. Principalele sisteme afectate de către sindromul metabolic și obezitate sunt sistemul circulator, sistemul digestiv cu particularitate asupra pancreasului și al ficatului, sistemul reproductiv și sistemul locomotor.

Cuvinte cheie: Porc miniatural Ossabaw, sindrom metabolic, obezitate

Metabolic syndrome is characterized by central (intra-abdominal) obesity, insulin resistance, impaired glucose tolerance, dyslipidemia and hypertension.

Ossabaw miniature swine living on Ossabaw Island, where food is abundant in the fall but scarce in the winter, developed the naturally selected "thrifty phenotype" that allows them to store large amounts of fat to survive the feast and famine ecology. This thrifty phenotype confers a propensity to long-term complications of food excess. Ossabaw swine allowed to eat excess food in captivity have the highest levels of total body lipid of any mammal and become morbidly obese even in the absence of a high-fat diet. Ossabaw miniature pigs fed an excess calorie diet high in fat, cholesterol, and fructose develop metabolic syndrome with its consequences (5, 11, 17, 18).

The main reason why we chose this subject is because of the similarity between the Ossabaw miniature pigs and humans regarding the metabolic syndrome. This minipig may be an extraordinary model that will enable a greater understanding of why the frequency of the metabolic syndrome and death related to coronary heart disease are increasing at such an alarming rate in humans, especially women, given the fact that primary insulin resistance and coronary disease develop in the Ossabaw female pigs (17). The pig is an extremely useful biomedical model for investigating potential treatment and prevention strategies for many human diseases. The minipig is considered the best breed for investigation on the metabolic syndrome (12).

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OSSABAW MINIATURE PIGS AND METABOLIC SYNDROME

The pig is an exceptional restenosis model and is emerging rapidly as a biomedical model for energy metabolism and obesity in humans because postnatal it is devoid of brown fat and because of their similar metabolic features, cardiovascular systems, and proportional organ sizes.Nowadays, obesity and the asso-

ciated chronic inflammation and insulin resistance are among the most prevalent diseases in developed countries (17). The morbid conditions related to obesity such as abdominal obesity, insulin resistance and glucose intolerance, hypertension and dyslipidemia are together called the metabolic syndrome. Recent evidence suggests that the intestinal microbiota is an important contributing factor to obesity and obesity-related metabolic disorders, known as the metabolic syndrome. Obesity-related changes in the composition of the intestinal microbiota were found in lean versus obese Ossabaw minipigs. In both pig models diet seems to be the defining factor that shapes the intestinal microbiota as observed by changes in different bacteria divisions between lean and obese minipigs (16). Human studies show that dietary fiber can prevent the different pathologies linked to the appearance of metabolic syndrome (1).

THE EFFECTS OF METABOLIC SYNDROME ON THE CIRCULATORY SYSTEM

Multiple studies have shown that the vascular disorders associated with the metabolic syndrome in miniature pigs involve atherosclerosis, vascular remodeling of arterial diameter, alterations in local blood flow supply, endothelial dysfunction, reduced nitric oxide concentration and increased vascular oxidative stress (3, 5, 6, 13, 14).

Given an atherogenic diet, mini pigs develop early neointimal hyperplasia of coronary arteries and mild hypertension. Bodyweight is also significantly higher in animals fed an excess high-fat and high-cholesterol diet and mean arterial blood pressure and heart rate are higher in obese Ossabaw swine (3, 5).

Recent studies implicate channels of the transient receptor potential vanilloid family (e.g., TRPV1) in regulating vascular tone. In lean pigs, capsaicin, a TRPV1 agonist found in chili peppers, relaxes arteries in a dose-dependent manner. Capsaicin-induced relaxation is blocked by the TRPV1 antagonist capsazepine. Capsaicin-induced relaxation is impaired in pigs with metabolic syndrome. Impaired capsaicin-induced vasodilation in the metabolic syndrome is associated with decreased expression of TRPV1 and cation influx (3).

In humans, there is a positive association between epicardial adipose tissue volume and coronary atherosclerosis burden.

Therefore, in a group of Ossabaw miniature swine fed with an atherogenic diet to produce coronary atherosclerosis, a coronary epicardial adipose tissue (cEAT) resection was performed. Resection of cEAT decreased the progression of coronary atherosclerosis, suggesting that cEAT may exacerbate coronary atherosclerosis (13).

THE EFFECTS OF METABOLIC SYNDROME ON THE LIVER

The hepatic manifestation of metabolic syndrome is considered to be the nonalcoholic steatohepatitis (NASH). It is characterized by intracellular lipid accumulation in hepatocytes, but it is not due to a secondary cause such as significant alcohol intake. NASH is characterized by lobular inflammation, hepatocellular ballooning, and pericellular fibrosis that can progress to cirrhosis. In humans, NASH is predicted to become the predominant cause of cirrhosis requiring liver transplantation in Western nations within the next two decades. Ossabaw miniature swine fed an excess calorie diet high in fat, cholesterol, and fructose develop metabolic syndrome with NASH (2, 10, 11).

Miniature pigs with NASH have mean body circumference significantly increased. Also, liver weight is significantly higher in these swine (11).

Biochemistry of mini pigs with metabolic syndrome and NASH display AST and ALT elevations, increasing serum cholesterol levels (in particular total and LDL cholesterol levels and LDL-to-HDL ratio) and triglycerides significantly raised. Also, blood glucose levels are higher in these patients (2, 11). Histological examinations of these pigs' liver show macrovesicular and microvesicular steatosis, fatty Kupffer cells, extensive hepatocyte ballooning, and pericellular or perisinusoidal fibrosis (2, 10; 11). Studies also show that the hepatic apoptotic index is significantly higher in miniature pigs with NASH (11).

THE EFFECTS OF METABOLIC SYNDROME ON THE PANCREAS

Several studies show that the breeds most susceptible to disorders of the pancreas associated with the metabolic syndrome are Iberian and Ossabaw miniature pigs (7, 19).

Ossabaw miniature swine fed with a modified atherogenic diet develop significant pancreatic steatosis and increased oxidative stress. The fructose diet which induces metabolic syndrome without changes in liver histology results in enlargement of some islets with lipid accumulation, but no other significant changes within the pancreas. The atherogenic diet, which induces metabolic syndrome and simple steatosis in the liver, also induces some islet enlargement and lipid accumulation in the pancreas. The NASH diet, however, induces severe metabolic syndrome and abnormal liver histology consistent with human NASH, along with islet enlargement and significant fat accumulation in the pancreatic tissue. The NASH diet group also exhibits significantly increased serum and pancreatic oxidative stress levels in the absence of cellular injury or inflammation in the pancreas.

There are no significant differences in amylase, lipase, glucose, or insulin values among any of the diet groups (7).

The effects on carbohydrate metabolism are found earlier than the effects on lipid metabolism. There are no significant differences in plasma glucose concentrations of Ossabaw miniature pigs as it has been described in humans. However, a high intake of saturated fat can cause impaired glucose regulation and induces some degree of insulin resistance and altered β-cell function, which are the main parameters of type 2 diabetes (19). It takes 5–6 months to develop the "obese-metabolic syndrome" phenotype but it may take many years to develop type 2 diabetes in some pigs and even then, it is not guaranteed that they will develop diabetes (8).

THE EFFECTS OF METABOLIC SYNDROME ON THE REPRODUCTIVE SYSTEM

Female mini pigs are more predisposed to developing metabolic syndrome than are male minipigs. When fed an excess-calorie, high-fat, high-cholesterol, high-fructose diet, female Ossabaw minipigs develop obesity, metabolic syndrome, and abnormal reproductive function. Obese minipigs have longer estrous cycles, higher serum androstenedione, and higher luteal phase serum luteinizing hormone. During the luteal phase, obese pigs have more medium, ovulatory, and cystic ovarian follicles, whereas normal weight pigs have smaller ovarian follicles. This animal model may also apply to studies of the effects of obesity on fertility in women (15).

THE EFFECTS OF METABOLIC SYNDROME ON THE SKELETAL MUSCLE

The fiber type composition of skeletal muscle has a strong effect on the metabolism and utilization of glucose and lipids. Not only fiber type composition but also the size of skeletal muscle fibers could have a major effect on muscle function.Increased fiber size could diminish oxygen and substrate supply for the metabolic processes in the central area of the fiber. High-fat and high-carbohydrate diets are known to induce accumulation of intramyocellular lipids (IMCL) in skeletal muscle fibers (4).

THE EFFECTS OF METABOLIC SYNDROME ON PLATELETS

Metabolic syndrome and type 2 diabetes mellitus in humans are associated with increased platelet activation and hyper-reactivity of platelets to various agonists. Ossabaw swine develop all the hallmarks of metabolic syndrome including obesity, insulin resistance, hypertension, dyslipidemia, endothelial dysfunction, and coronary artery disease when being fed excess calorie atherogenic diet. Metabolic syndrome in Ossabaw swine is associated with increased reactivity of platelets to adenosine diphosphate (ADP) and collagen. No significant difference is found for platelet aggregation in response to thrombin (9).

CONCLUSIONS

Metabolic syndrome in Ossabaw miniature pigs manifests through morbid obesity, atherosclerosis with high blood pressure, type 2 diabetes with insulin resistance and altered β-cell function, pancreatic steatosis with increased oxidative stress, nonalcoholic steatohepatitis, dyslipidemia, abnormal reproductive function of females with longer estrous cycles caused by cystic ovarian follicles, accumulation of intramyocellular lipids in skeletal muscle fibers,endothelial dysfunction and increased platelet activation with hyperreactivity of platelets to adenosine diphosphate and collagen.

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