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THE IMPORTANCE OF REGULATION DIGESTIVE SYSTEM – BRAIN INTERACTIONS ON PREVENTION INSULIN RESISTANCE AND FATTY LIVER

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Abstract
Introduction: Obesity, insulin resistance (IR) and fatty liver (FL) related to modern lifestyle are getting epidemic characteristics and present the most important world public health problem. Obesity, FL and IR are basic parts of metabolic syndrome. Metabolic syndrome is caused by excessive consumption of high-calorie food, chronic stress and unhealthy eating behavior. Current research shows that the digestive system with close realationship with brain has central role for keeping entire health and plays a fundamental role in pathogenesis of insulin resistance and fatty liver, but and many other diseases.
Aim of the work: The aim of the paper is to evaluate and summarize new knowledge about relationship between the digestive system and the brain and how disregulation of interaction among them and eating behavior can influence on development IR and FL. Next aim of the work is to find evidence of positive effect of implementation new recommendations for healthy eating behavior, the current dietary and physical activity guidelines on prevention insulin resistence and fatty liver.
Results: Current science has shown that food, eating habits and digestive system-brain relationship have a strong and decisive influence on patogenesis insulin resistance and fatty liver. Choosing healthy personal diet and healthy eating habits with a healthy lifestyle gives the opportunity to prevent insulin resistence and fatty liver, cardiovascular diseases, diabetes mellitus and many other diseases
Conclusion: Better understanding of new key mechanisms of development insulin resistance and fatty liver lead to the development new therapeutic dietary and nutritional approaches. IR an FL have asymptomatic clinical course, so primary prevention and screening in early childhood are the best way to prevent the beginning and expansion of diseases. Current treatment needs to be based on the principles of personal medicine and focused on healthy lifestyles including nutrition and physical activity.

Key words: Digestive system- brain interactions, eating behavior, fatty liver, Insulin resistance, prevention.

ZNAČAJ REGULACIJE INTERAKCIJE IZMEĐU PROBAVNOG SUSTAVA I MOZGA NA PREVENCIJU INZULINSKE REZISTENCIJE I MASNE JETRE

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Sažetak
Uvod: Pretilost, inzulinska rezistencija (IR) i masna jetra (FL) povezani sus modernom načinom života, te poprimaju sve karakteristike epidemije i predstavljaju najvažniji svjetski zdravstveni problem. Pretilost, FL i IR su sastavni dijelovi metaboličkog sindroma. Metabolički sindrom je uzrokovan pretjeranom potrošnjom visokokalorične hrane, kroničnog stresa i nezdravog ponašanja tijekom prehrane. Suvremena istraživanja pokazuju da jeprobavni sustav blisko povezan s mozgom, te ima središnju ulogu u održavanju cijelovitog zdravlja i temeljnu ulogu u patogenezi inzulinske rezistencije i masne jetre, ali i mnogih drugih bolesti.
Cilj rada: Cilj rada je procijeniti i sažeti nova znanja o odnosu između probavnog sustava i mozga te prikazati kako regulacija interakcije između njih i ponašanja u prehrani može utjecati na razvoj IR i FL. Sljedeći cilj rada je ukazati na dokaze pozitivnog učinka primjene novih preporuka zdravih prehrambenih navika, smjernica o prehrani i tjelesnoj aktivnosti na prevenciji inzulinske rezistencije i masne jetre.

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Rezultati: Trenutna znanost je pokazala da hrana, prehrambene navike i odnos probavnog sustava i mozga imaju jak i odlučujući utjecaj na patogenezu inzulinske rezistencije i masne jetre. Odabir zdrave osobne prehrane i zdravih prehrambenih navika sa zdravim životnim stilom daje mogućnost da se spreveniraju inzulinska rezistencija i masna jetra, kardiovaskularne bolesti, dijabetes melitus i mnoge druge bolesti.
Zaključak: Bolje razumijevanje novih ključnih mehanizama nastanka inzulinske rezistencije i masne jetre dovodi do razvoja novih terapeutskih dijetetskih i prehrambenih pristupa. Inzulinska rezistencija i FL imaju asimptomatski klinički tijek, tako da je primarna prevencija i screening u ranom djetinjstvu najbolji način da se spriječi početak i razvoj bolesti. Trenutačna terapija mora se temeljiti na načelima osobne medicine i biti usmjerena na zdrav stil života, uključujući prehranu i tjelesnu aktivnost.

Ključne riječi: interakcije probavnog sustava i mozga, ponašanje u prehrani, masna jetra, inzulinska rezistencija, prevencija.

Intraduction

Life and health are directly depend by the food, normal digestive function, healthy lifestyles and eating behavior. The new concept of relationships among the brain, eating behavior and digestive system provide new insights into the etiopathogenesis of insulin resisistance, fatty liver and new oportunity for prevention (IOM, 2015; Salihefendić and Zildžić 2016).

Digestive function has five integrates phases: ingestion, propulsion, digestion, absorption and defecation and every phase is under control "two brains" (main brain and gastrointestinal enteric nervous system).For keeping health it neceserry to provide healthy food- personal diet, adequate control of „two brain" and synchronisation of all five phasese of digestion (IOM, 2015; Salihefendić and Zildžić 2016; Lam et al.,2019)

When food enters the mouth, the digestive system sends many signals to both of the brain.

In mouth mechanical digestion begins with chewing and food mixing with saliva which contains digestive enzymes. In oral cavity there are many receptors. Taste receptors in oral cavity, taste cells and taste like cells produce many signaling proteins. They play important role in integrating physiological response during whole digestion.

Food in stomach sends signals and information about volume and quantity trough nerve vagus afferent path. The most important information about quality of food, nutrient content and antigens structure have been sent in the brain by small intestine. Two phases (digestion and absorption) which happened in the small intestine are critical point for development metabolic disorders. The gut has sensory, neuroendocrine and immune function in the body (IOM, 2015; Lam et al., 2019).

Defecation does not have so active metabolic function but it is necessary part of efficient complete digestion. The large intestine is place with very intensive exchange of information with the brain and can be important cause of maldigestion (IOM, 2015).

Relationship between the brain and digestive system

When food passes through the digestive system sends great number signals and information about volumen, nutrient content and its structures The brain receives much of those informations through the nerve vagus. Interaction between nutrients from food and different gens and receptors in digestive system can leads to the health or disease.

The intistine and mesentery have they own brain – the enteric nervous system which contributes in overall digestive function and exchanges informations with the main brain (IOM, 2015; Salihefendić and Zildžić 2016). This complex signaling feedback system starts in oral cavity where taste cells in the thongue send first information in the hindbrain (nucleus tractus solitarii). Taste-like cells are indentified in the stomach, the intestine and in the pancreas.Those cells release neurotransmiters and neuropeptide hormones in the blood and with the brain they regulate the process of satiation. Presence of food in the gut triggers signals to the brain about volumen,content, nutrient and character.Those information have great impact for further intake. Vagal afferent signal activated by gut peptides like cholecystokinin (CCK) contribute to the process of satiation through releasing glutamate in the hindbrain (" the feeling of satiety"). Proteins from white-visceral fat tissue, such as leptin can also contribute to the process of satiation (IOM, 2015; Lam et al.,2019)

GI signaling peptides controle food intake, gastric emptyng, secretion of enzymes, but and insulin secretion and sensitivity. For this function the intestinum needs normal composition of microbioma. Eating is impacted by much more factors than what happens when food enters in the body and triggers

feedback signals to the brain. Visceral adipose tissue, the mesentery and liver (adiponectines) provide the main brain with important informationes about process of digestion and metabolism. This function can influence on eating beahavior and food intake (Sai et al., 2016).

Visceral fatty tissue and the mesentery

Adipose tissue is the physiological site of storage energy. It has been more recently recognized as an active endocrine organ (Bradley et al., 2011; Bastard et al., 2006). The mesentery fatty tissue has a neuroendocrine function through mediators called adipocytokines, of which: adiponectin, leptin, resistin, and ghrelin are the most important. They play an important role in neuroendocrine control of the entire body's function and digestion with close relationship with the brain. Feelings of hunger, satiation, food cravings, and food avoidance, and eating behavior are influenced by the gut and the mesentery. They produce neurotransmitters, especially serotonin, which enhance mood and cognitive process. Mesenteric glands form an important part of immune response.Visceral white fatty tissue (VFT) produce many mediators called adipocytokines and wide range of inflammatory mediators including TNF-alpha and interleukin-6 (IL-6). Infiltration of VFT with macrophages leads to chronic infection with systemic effects on all body tissue and contribute to the pathogenesis of IR and FL. Leptin could modulate TNF-alpha production and macrophage activation. Level of adiponectin is decreased in subjects with obesity-related insulin resistance, type 2 diabetes and coronary heart disease. Adiponectin inhibits liver neoglucogenesis and promotes fatty acid oxidation in skeletal muscle. Chronic inflammatory condition promotes the production of pro-inflammatory factors involved in the pathogenesis of insulin resistance (Bradley et al., 2011; Bastard et al., 2006; Galic et al., 2010; Lee et al., 2010).

Insulin resistance

Insulin resistance (IR) makes body cells less sensitive to insulin, so the pancreas has to produce more and more insulin to keep normal blood glucose levels. Insulin resistance is epidemic condition, more than 50% of population suffer some degree of insulin resistence. It is background and key point for development of majority chronic diseases.Insulin affects the function of all body tissues. Insulin has relevant functions as neuromodulator in CNS (eating behaviors, cognitive process) and in cardiovascular physiology. Insulin affects the function of all endocrine organs. Polycystic ovary syndrome is strongly associated with IR.The liver, the visceral adipose tissue and the gut play important role in the development of insulin resistance, obesity and diabetes mellitus (Sai et al., 2016; Bastard et al., 2006; Lee et al., 2010)

The liver as central metabolic organ has functional and anatomic connection with the gut and the mesentery visceral adipose tissue.They interaction is important mechanism for keeping health, but in oposite main cause and site for metabolic disorders. A recent review proposed that IR and fatty liver arise as a consequence of many parallel disorders in intrinsic and extrinsic cellular mechanism. Intrinsic disorders include mitochondrial dysfunction, oxidative stress and endoplasmic reticulum stress. Extrinsic disorders include alterations in secretion of cytokines, adipokines (hepatokines) and proinflamatory mediators originating from visceral adipose tissue, liver and gut. An increase in circulating levels of these macrophage-derived factors in obesity leads to a chronic low-grade inflammatory state that has been linked to the development of insulin resistance and diabetes (Lam et all; Bradley et al., 2011; Konrad et al., 2014; Jin et al., 2013)

Fatty liver

Fatty liver (FL), steatosis or non-alcoholic fatty liver disease (NAFLD) is a metabolic disorder characterized primarily by the accumulation of fat droplets in the hepatocytes, with no data on alcohol consumption, infections or autoimmune disorders (Salihefendić and Zildžić, 2016).

Disease occurs in a wide range of hepatic stages of activity (simple steatosis FL, non-alcoholic steatohepatitis -NASH, fibrosis and cirrhosis with possible progression to hepatocellular carcinoma) (Firneisz, 2014)- NAFLD is associated with the obesity and IR, but also with a series of clinical extra-hepatic events including cardiovascular disease, type 2 diabetes mellitus, endocrine and mental disorders (Bush et al., 2017). Fatty liver occurs in all age groups. High body mass index (BMI), abdominal fat and viscerally hypertrophied fatty tissue are predictive important factors for the development of fatty liver with all hepatic and extra hepatic manifestations. The prevalence of pathologic obesity and fatty liver in the general population is high and takes epidemic characteristics ("pandemic of the new millennium") (Firneisz, 2014)

Relationships among the brain, the digestive system and eating behavior

Food intake and eating behavior in the proper manner play an important role in metabolic process and energy homeostasis. Eating behavior can improve all phases of digestion, but disorders in eating behavior lead to derange of interactions between the brain and digestive system. (IOM, 2015; Sai et al., 2016; Lee et al., 2010).

The psychosomatic theory about eating behavior emphasizes cognitive control of eating style. If this cognitive control is disrupted by stress new eating style has negative influence on all digestive process. The Dutch Eating Behavior Questionnaire is an internationally widely used instrument assessing different eating styles that may contribute to obesity and IR: emotional, external and restraint eating. Emotional stress leads to increase of appetite and food intake. (Hilbert at all,2012)

Practical aapproach to prevention IR and FL

Practical management is related to two way: 1. reduce need for insulin (special modifying diet for reduce secretion and insulin resistance and modifying eating styles) 2. Increase cells sensitivity to insulin. (physical activities, medication as metformin and others, food supplements (verbal), eating styles and lifestyles modification) (Mercurio et al., 2012;Goutham 2001)

For primary prevention of IR and FL is necessery to folow next recommendations :1.Choosing healthy personal diet; 2. Eating on regular schedule; 3. Chewing food well; 4. Drinking enough water; 5. Incorporation of: fiber, prebiotics ant probiotics in diet; 6. Managing stress and negative emotions; 7. Limiting an amount of food (3/4 of gastric capacity); 8. Limiting iced beverages; 9. Eating slowly; 10. Sitting down, enjoying meal; 11. Avoidance of any others activity during meal time like: watching TV, reading etc., and 12. Avoidance physical activity following meal time) can improve brain-digestive system interaction and enables synchronic digestion. (Mercurio et al., 2012;Goutham 2001)

When discussing physical activity with patients, the discussion should focus to enable to patient to increasing physical activity and finding ways for patients to incorporate exercise into their lives on a regular basis. It is helpful to separate the benefits of exercise from weight loss. Physical activites have its own benefits in terms of a sense of well-being and improved insulin resistance. Studies have also shown that losing relatively small amounts of weight in the range of 5% to 10% make significant benefits in terms of IR and FL The prospective cohort study demonstrated that walking briskly for 1 hour daily reduced the risk of developing obesity and IR. Caloric restriction, healthy personal diet and moderate exercise led to improved stage of FL. (Salihefendić and Zildžić, 2016; Mercurio et al., 2012;Goutham 2001)

Conclusion

Current science has shown that food, eating behevior and digestive functions have a strong and decisive influence on life, quality of life, and on the appearance of various diseases. The interaction of the ingredients in food in first contact with human-specific digestive system and specific genomes have far reaching consequences that people are not yet aware of. Choosing healthy personal diet and healthy eating behavior with modification lifestyles gives the opportunity to prevent development IR and FL and diseases connected with them, as well as improving the quality of life.

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