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GUT MICROBIOTA AND DIABETES REMISSION AFTER METABOLIC SURGERY

Sažetak: U gastrointestinalnom traktu čoveka postoji više od 200 vrsta bakterija sa različitim genomima koji učestvuju u degradaciji ugljenih hidrata, sa glavnom ulogom u varenju hrane. Dominantne bakterije razgrađuju složene ugljene hidrate i oslobađaju masne kiseline kratkih lanava (SCFA) koje su izvor energije, sinteze holesterola i glukoneogeneze. Međusobna interakcija crevnih bakterija i imunog sistema neophodna je za održavanje ovog simbiotskog odnosa. Zastupljenost crevnih bakterija se razlikuje u različitim metaboličkim stanjima. Betaproteobacteria i Firmicutes dominiraju u crevima gojaznih osoba, dok Akkermansia muciniphila smanjuje gojaznost, inflamaciju niskog stepena i insulinsku rezistenciju. Intestinalna disbioza je udružena sa insulinskom rezistencijom i dijabetesom tipa 2. Odnos of Bacteroidetes i Firmicutes kao i odnos Bacteroides-Prevotella grupe prema C.coccoides-E.rectale grupi je smanjen. Promena anatomskih odnosa u gastrointestinalnom traktu nakon gastričnog bajpasa uzrokuje i značajnu promenu crevne flore. Manipulacija crevnim bakterijama koja povećava zastupljenost Akkermansia spp. Može da poboljša efekat metformina. Promena crevnih bakterija posle RYGB (Roux-en-Y gastric bypass) utiče povoljno na smanjenje telesne mase, nezavisno od drugih efekta barijatrijske/metaboličke hirurgije.

Mehanizam remisije dijabetesa posle barijatrijske hirurgije još nije sasvim razjašnjen. Osim promene inkretinskog efekta i recirkulacije žučnih kiselina, moguće je da promena crevne mikrobiote igra značajnu ulogu

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u remisiji što bi moglo da bude povezano sa proizvodnjom butirata i propionata od strane pojedinih bakterijskih speciesa.

Abstract: Humans carry up to 200 bacterial species in the gastrointestinal tract. Important contribution of these genes is in carbohydrate degradation. The main task of the gut microbiota is digestion of food. The dominant gut bacteria are degraders of complex polysaccharides and releasing SCFA which are the sources for energy, cholesterol synthesis and gluconeogenesis.

The mutual interaction of gut microbiota and host immune system is necessary for maintaining their symbiotic relationship. Microbial compositions differ in different metabolic conditions. *Firmicutes* are dominant in obese subjects while *Akkermansia muciniphila* which protect against adiposity, low grade inflammation in adipose tissue and insulin resistance is reduced in this population. Intestinal dysbiosis is associated with insulin resistance and diabetes type 2. Betaproteobacteria was highly enriched in diabetic population. The ratio of *Bacteroidetes* to *Firmicutes* and the *Bacteroides-Prevotella* group to the *Clostridiales-Eubacterium* group are reduced. Gastrointestinal rearrangements after RYGB promote substantial changes on the gut microbiota. Gut microbiota manipulation in favor of *Akkermansia spp.* may contribute in antidiabetic effect of metformin and could be potential treatment for T2D. Changes in gut bacteria after RYGB (Roux-en-Y gastric bypass) alter the body weight independent of other effects of bariatric/metabolic surgery.

Mechanism for diabetes remission after bariatric surgery is still not clear. Besides change in incretin secretion and bile acid recirculation, potential mechanism is change of gut microbiota content. Possible improvement of glucose regulation following bariatric surgery may be related to butyrate and propionate production by some bacteria species, which influence glucose metabolism independently of bile acids recirculation.

Human guts are colonized by biomass of 1kg or 100 trillion microbes. Gut microbes play a roles in degradation of nondigested polyccharides to SCFA (short chain fatty acids), productions of vitamins B 12 and K and bile acids biotransformation (1).

Humans carry up to 200 bacterial species in the gastrointestinal tract with unique genome in each species. Important contribution of these genes is in carbohydrate degradation. Human host produces 17 carbohydrate active enzymes and gut bacteria have more than 200 carbohydrate enzymes (2,3). The main task of the gut microbiota is digestion of food. The dominant gut bacteria are degraders of complex polysaccharides and releasing SCFA. The most abundantly produced SCFA are acetate, propionate and butyrate. This products are sources for energy, cholesterol synthesis and

gluconeogenesis. The mutual interaction of gut microbiota and host immune system is necessary for maintaining their symbiotic relationship (4).

The colonisation and maturation of the newborn GIT begins at birth and continues for two years. The gut microbiome development depends of the mode of the delivery, feeding regime, maternal weight, prebiotic, probiotic and antibiotic use (5,6). Some studies have examined the impact of cesarean section on the development of obesity in the childhood. The first contact of the fetus with microorganisms occurs during delivery. The bacterial communities colonize the intestine from maternal vaginal and fecal microbiota (facultative anaerobic bacteria which consume oxygen and make an anaerobic environment) during vaginal delivery or from the maternal skin bacteria in case of C-section delivery. C-section delays colonization by *Lactobacillus*, *Bifidobacterium* and *Bacteroides spp.* Chinese study had shown the association between C-section, maternal BMI and higher risk for overweight. The study of American children born by C-section demonstrated that those children had twice the like hood to be overweight or obese. Some meta-analyses also have similar conclusions that C-section in comparison with vaginal delivery was associated with higher risk for obesity in children, adolescents or adults (7). Recent findings suggests that gut microbiota plays a pivotal role in energy homeostasis as well as in the development of obesity, progression of excessive fat storage and obesity related metabolic disorders (8).

The gut bacteria enhance adiposity mainly by increased energy extraction from food and by regulating fat storage (9). Colonic propionate decrease energy intake and prevent long-term weight gain (10). An obese type microbiota shows higher triglyceride storage in adipocytes and lower expression of satiety. Diet induced obesity and associated inflammatory disorders may result from dysbiosis of gut microflora and dysregulation of endocannabinoid system. Lipopolysaccharides cause production of endogenous ligands of cannabinoid receptors which provoke hyperglycemia and insulin resistance and induce chronic inflammation in visceral fat. Microbial compositions differ in different metabolic conditions. *Firmicutes* are dominant in obese subjects while *Akkermansia muciniphila* which protect against adiposity, low grade inflammation in adipose tissue and insulin resistance is reduced in this population (9,11). Intestinal dysbiosis is associated with insulin resistance and diabetes type 2 (12).

Betaproteobacteria was highly enriched in diabetic population. The ratio of *Bacteroidetes* to *Firmicutes* and the *Bacteroides-Prevotella* group to the *C.coccoides-E.rectale* group are reduced (13). High levels of LPS (lipopolysaccharide) and pro-inflammatory cytokines are responsible for metabolic endotoxemia and low-grade inflammation(14). LPS triggers the inflammatory cascade with proinflammatory cytokines such as IL-6, IL-1 and TNF which inhibit the phosphorylation of insulin receptors (15).

Gastrointestinal rearrangements after RYGB promote substantial changes on the gut microbiota. Gut microbota manipulation in favor of *Akkermansia spp.* may

contribute in antidiabetic effect of metformin and could be potential treatment for T2D (16). Changes in gut bacteria after RYGB (Roux-en-Y gastric bypass) alter the body weight independent of other effects of bariatric/metabolic surgery. That was approved with fecal transplants from RYGB treated mice to sham-treated obese mice (17,18). Mechanism for diabetes remission after bariatric surgery is still not clear. Besides change in incretin secretion and bile acid recirculation, potential mechanism is change of gut microbiota content. Based on previous findings there was a tight connection between altered *Firmicutes/Bacteroidetes* ratio and postoperative diabetes remission as well as diabetes recurrence (19). Possible improvement of glucose regulation following bariatric surgery may be related to butyrate and propionate production by some bacteria species, which influence glucose metabolism independently of bile acids recirculation (1). One study demonstrated abundance of *Lactobacillus crispatus*, which is with *Streptococcus species* the major lactic acid producing bacteria. There are also *Megasphaera elsdenii*, bacteria which utilizing lactate and reduce lactate toxicity by producing propionate, butyrate and propionate (20). *Gammaproteobacteria* was not found in subjects before surgery could have metabolic impact (21). Increased diversity of more than half of gut bacteria with weight reduction and glucose improvement at least three months after RYGB indicating that bariatric surgery results in rapid shifts in gut microbiome (22).

Laparoscopic sleeve gastrectomy (LSG) is characterized by decreased of *Eubacterium rectale*, *Bacteriodes spp*, *Lachnospiraceae* and *Clostridium spp*. Gut microbiota modulating bile biosynthesis and biotransformation of bile acids while bile acids, as a detergent, inhibit bacterial growth. Bile acids change the bacterial content in the gut through signaling pathways FGF19, GLP-1, GLP-2, PYY and G protein coupled receptor. This may be one of underlying mechanisms for diabetes remission after metabolic surgery (22).

One more substance forms in the liver from trimethylamine (TMA) is Trimethylamine-N-oxide (TMAO), a product generated by gut microbiota from carnitine and phosphatidylcholine. The sources of these metabolites are dairy products, eggs and red meat. Some studies investigated the role of TMAO in obesity and T2D. The increase in TMAO was seen in patients after RYGB and duodenal switch. Increase in *E.coli* and *Pseudomonas* which use TMAO, support conversion TMA in TMAO and thus elevated levels of TMAO which may have impact on T2D remission after surgery (23).

There are some new bacteria discovered after bariatric surgery such as *Eisenbergiella masiliensis* (within the *Lachnospiraceae* family in the phylum *Firmicutes*) and *Anaerotuncus* (*Clostridiaceae* family, also the phylum *Firmicutes*) which increase energy expenditure and support weight loss and metabolic effect of malabsorptive bariatric procedures (24,25).

Change in gut microbiota with bile acids causes significant incretin effect in RYGB (26).

Bariatric procedures helps to define possible link between glucose and lipid metabolism and metabolic activities of gut microflora (21,27,28). The role of gut microbiota on glucose metabolism after bariatric surgery is not fully understood and needs further investigation.

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