PROCEEDING BOOK

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" IMPROVING MANAGEMENT OF ENDOCRINE DISORDER IN CLINICAL PRACTICE "

Ruang Widyasabha
Lt 4 Fakultas Kedokteran
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DAFTAR ISI

GUT MICROBIOTA AND METABOLIC DISORDERS

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Adult human gut is populated with as many as 10^{13}-10^{14} cells, mostly bacteria as well as fungi, viruses, and other microbial and eukaryotic cells.[1,2] More than a thousand of different bacterial species is known to colonize the human gut, and it is well established that five bacterial phyla, *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*, are the dominant components.[3] More than 90% of the bacterial populations are gram-negative anaerobes including the predominant genera *Bacteroides*, *Eubacterium*, *Bifidobacterium*, and *Fusobacterium.*[4] The microbiota is involved in numerous important physiological functions such as digestion, micronutrient production, restriction of growth of potentially harmful bacteria, and development of the immune response.[5]

The gut microbiota plays an important role in the regulation of the host's metabolism and the extraction of energy from ingested food. Not only the beneficial functions for the host, the gut microbiota also exert the pathophysiological interactions with the host, particularly in the case of obesity and related metabolic disorders. Recent findings have suggested that an altered gut microbial composition is associated with metabolic diseases, including obesity, diabetes, or non-alcoholic fatty liver disease. These findings have indicated that the gut microbiota should be considered as an important factor in modulating host metabolism and related metabolic disorders.

Ley et al. (2005) reported the relationship between gut microbiota and metabolic diseases. It was reported that leptin-deficient mice (ob/ob), contained fewer B*acteroidetes* and more *Firmicutes* than control mice.[6] Furthermore, a follow-up study also observed similar shift in *Bacteroidetes* and *Firmicutes* ratio between obese human subjects and their lean counterpart.[7] However, some researchers reported no shift in the ratio of *Bacteroidetes* and *Firmicutes* in human subjects with weight loss.[8-10]

The advance of microbiota transplantation experiment has led us to further elucidate the relationship between the gut microbiota and related metabolic disorders. It was reported that germ-free (GF) animals are protected against the obesity that develops after consuming a Western-style, high-fat, sugar-rich diet.[11] Interestingly, colonization of adult germ-free C57BL/6 mice with a normal microbiota harvested from the distal intestine (cecum) of conventionally raised animals produces a 60% increase in body fat content and insulin resistance within 14 days despite reduced food intake.[12] It was revealed that the microbiota promotes absorption of monosaccharides from the gut lumen, resulting in induction of de novo hepatic lipogenesis. It was also found that Fasting-induced adipocyte factor (Fiaf) is selectively suppressed in the intestinal epithelium of conventionalized mice. This finding provides the mechanistic evidence that microbes could increase the storage of host's body fat.

Dysbiosis is a condition where microbial communities in the intestinal tract cause detrimental effects due to their quantitative and qualitative changes in composition, distribution and metabolic activities.[13] Recently, some observasional studies found the relationship between

dysbiosis and the risk of metabolic disorders. In human it was found that dysbiosis in early stage of life correlate with the risk of overweight later in adolescent.[14-18] Antibiotic exposure is one of the common and significant factors that cause intestinal dysbiosis.[19] Changes in gut microbial composition followed by incomplete recovery was observed after administration of antibiotics.[20-23] Early-life period (under 3 years of life) is a critical period for metabolic development, thus gut microbial disturbance during this period of life could trigger body composition imbalance later in life.[24]

Despite of studies demonstrating the role of intestinal microbiota in the regulation and pathogenesis of metabolic disorders, due to the complexity of the microbial community, the underlying molecular mechanisms by which the gut microbiota regulate host's metabolisms and associated with metabolic disorders still poorly understood. An essential role of gut microbiota is the fermentation of undigestable dietary polysaccharides. enzymes secreted by the gut microbiota digested these fibers into short-chain fatty acids (SCFAs i.e. butyrate, acetate, and propionate) which will used by the host as energy source. SCFAs also function as regulators of energy intake[25] and inflammation.[26] SCFA promote intestinal gluconeogenesis,[27] incretin formation which subsequently increased satiety and reduced food intake.[25] SCFAs also mediated the suppression of insulin signaling in the adipose tissue with subsequent prevention of fat accumulation.[28] Disruption of the gut barrier function and the gut microbiota-derived endotoxemia (metabolic endotoxemia) also contribute to the pathogenesis of obesity and T2DM.[29] Disruption of the gut barrier increased gut permeability, increased absorption of lipopolysaccharide into the portal blood circulation, causing metabolic endotoxemia. Increased gut permeability due to reduced expression of tight junction protein was obsereved in the intestinal epithelial cells of high-fed diet mice.[30]

Even though obesity and metabolic diseases are principally considered as nutrition-related disorders, recent evidences indicate that the intestinal microbiota has an important role in development of metabolic disorders. Considering the gut microbiota as a factor contributing to development of metabolic disorders represents a tool of great therapeutic potential. However, further research in more complex animal models and human subjects is needed to provide any strategy aimed in modulating the human gut microbiota as a prevention or therapeutic tool for related metabolic disorders.

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