Study on gut microbiome and metabolome of Indonesian people in relation to dietary habits and metabolic diseases

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Title　：Study on gut microbiome and metabolome of Indonesian people in relation to dietary habits and metabolic diseases
(食習慣や代謝疾患に関連したインドネシア人の腸内マイクロバイオームおよびメタボロームについての研究)

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Thesis Summary

Since gut microbes interact with host immune and hormonal systems via cell components or metabolites, alterations of the gut microbiota and its function may be crucially involved in metabolic diseases. Global change in economy causing a shift in dietary habits of Asian people from their traditional style to modern style accompany with their specific genotype and phenotype accelerate them to simply take the high risk of obesity and type 2 diabetes (T2D). Indonesia is the country where the people suffering from obesity and T2D are increasing drastically under the shift in life and dietary styles. Moreover, gut microbiota and its metabolites of Indonesian people, associated with these metabolic diseases and diets, are worthy investigating to gain insight into the impact of the changing dietary style on the gut health of people in Asian developing countries. To this end, a pilot-scale cross-sectional study in Yogyakarta City as a representative of a developing city in Asia was performed.

To capture the status of Indonesian gut microbiome associated with obesity and T2D, fecal microbiome profiles from 75 Indonesian adults who lived in urban area of Yogyakarta City were investigated. Variations of microbiome indicated a triangular distribution in the principal component analysis, driven by three dominant bacterial genera, namely *Bacteroides*, *Prevotella*, and *Romboutsia*. The *Romboutsia*-overgrown microbiome, characterized by low bacterial diversity, was associated with obesity. The *Bacteroides*-defined microbiome, which counteracted *Prevotella* but was associated with Ruminococcaceae, showed positive correlation with T2D indices but negative correlation with body mass index (BMI). Anti-diabetic drug, metformin, showed alteration of Indonesian gut microbiome, including lactic acid and butyrate-producing bacteria. Notably, *Bacteroides fragilis* was increased in T2D patients, while it disappeared in patients administered metformin. These results indicate that the gut microbiome status of Indonesian subjects is differently associated with obesity and T2D.

To investigate the effects of dietary habits of Indonesian subjects on their gut microbiota associated with obesity and T2D, the seven-day dietary records from the subjects were analyzed in relation to gut microbiome profiles. The results revealed that Indonesian subjects had high fat consumption rate that is close to the maximum of WHO recommendation, especially the obese subjects who showed over than the recommendation. Fat consumption was associated with BMI in non-T2D subjects, but not in T2D subjects, that is probably due to the effect of dietary restriction or impaired metabolic status of the T2D patients. Association between macronutrients and gut microbiome profiles showed that *Romboutsia* overgrown in obese patients was positively correlated with fat consumption,

while Ruminococcaceae, trended to be co-abundance with *Bacteroides*, were positively correlated with carbohydrate consumption but negatively correlated with BMI, taken together with other two species, *Coprococcus* sp. and *Oscillibacter valericigenes*. These results suggest that fat consumption of Indonesian subjects is associated with the risk of obesity.

To study the linkage of gut metabolome and microbiome profiles to metabolic diseases in the Indonesian subjects, fecal short chain fatty acids (SCFAs), succinate, and bile acids (BAs) were investigated. As a result, fecal SCFAs and succinate were not different in obese and T2D groups. However, interestingly, level of succinate was positively correlated with *Romboutsia* abundance and was markedly high in non-T2D obese subjects. This result is a line of this study that shows non-beneficial aspects of bacteria-derived succinate that overrepresented in the obese subjects with gut dysbiosis. Fecal BA profiles between obese and T2D groups were distinguishable. The obese group had high levels of primary BAs and low levels of 7α-dehyroxylated BAs. The T2D group, harboring high abundance of *B. fragilis*, showed low levels of conjugated BAs, especially tauroursodeoxycholic acid (TUDCA), the farnesoid X receptor (FXR) antagonist with anti-diabetic activity, while these features disappeared in patients administered metformin. These results suggest how gut metabolites are involved in obesity and T2D in the Indonesian subjects. Particularly BA metabolism from native conjugative form to modified 7α-dehyroxylated form are differently characterized in obese, T2D, and healthy subjects.

In conclusion, this study indicates two types of gut microbiota, each of which is differently associated with obesity and T2D. High-fat diet-driven Indonesian obesity is associated with *Romboutsia*-overgrown gut microbiome dysbiosis with the loss of intestinal secondary BAs in association with a decrease in commensal Ruminococcaceae. T2D in the Indonesian subjects is associated with an increase in *Bacteroides* with the loss of conjugated BAs known to have anti-diabetic activity, and this alteration is reversed in patients receiving metformin treatment. Taken together, the altered fecal BA profiles in Indonesian subjects represent gut microbiome status linking host metabolic disorder.