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Losing weight for a better health: Role for the gut microbiota

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SUMMARY

In recent years, there have been several reviews on gut microbiota, obesity and cardiometabolism summarizing interventions that may impact the gut microbiota and have beneficial effects on the host (some examples include [1–3]). In this review we discuss how the gut microbiota changes with weight loss (WL) interventions in relation to clinical and dietary parameters. We also evaluate available evidence on the heterogeneity of response to these interventions. Two important questions were generated in this regard: 1) *Can response to an intervention be predicted?* 2) *Could pre-intervention modifications to the gut microbiota optimize WL and metabolic improvement?* Finally, we have delineated some recommendations for future research, such as the importance of assessment of diet and other environmental exposures in WL intervention studies, and the need to shift to more integrative approaches of data analysis.

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1. Weight loss interventions, health outcomes and the role for gut microbiota

1.1. Effect of calorie restriction on gut microbiota – can we predict host responses based on pre-intervention health status and microbiota composition?

Several studies in animal models and humans have addressed the impact of WL through calorie restriction (CR) on microbiota composition and its association with clinical outcomes (reviewed in [1–3]). Some of these studies have analyzed whether certain phenotypes before WL may impact or predict the effect of the intervention on health outcomes.

1.1.1. Rodent models

Studies in rodent models have shed light on the role that gut microbiota may be playing in obesity. It has been demonstrated in rodents that an obese phenotype can be transmitted via the microbiota. Gut microbiota, depending on its composition and function, may be involved in several mechanisms leading to fat mass gain and eventually obesity. Among these mechanisms the role of energy harvest from food (shown to be more efficient in certain bacterial groups) has been proposed. Germ free mice are resistant to diet-induced obesity [6,7], but gain weight upon transfer of gut microbiota from conventionally raised mice or *ob/ob* mice, potentially through increased capacity for energy harvest [8]. Gut microbiota may also impact host metabolism in the development of rodent obesity through the induction of hepatic lipogenesis, and suppression of *Fiaf* in the gut epithelia, leading to upregulation of LPL activity and increased fat storage [6]. There is also a direct interaction between the gut microbiota, the gut-associated immune system, and adipose tissue through metabolic endotoxemia [9–11]. Therefore, other effects such as the regulation of lipogenesis and gluconeogenesis, gut hormone secretion and induction of inflammatory response have also been demonstrated in rodents [5]. In addition, rodent models have been used to investigate the relationship between genetics and gut microbiota [12], and these studies have shown that different genetic backgrounds can lead to very diverse host–environment interactions.

Gut microbiota changes due to CR can be significant and depend on the type of intervention. For example, duration of CR can impact both gut microbiota composition and health outcomes. Zhang et al. showed in mice that lifelong CR led to large and consistent changes in gut microbiota composition [13]. In this study, there was lower midlife serum LPS binding protein (LBP, a surrogate of metabolic endotoxemia) in mice fed a low fat and calorie diet, as opposed to other dietary compositions. Phyla that inversely correlated with LBP were positively correlated with lifespan, emphasizing the importance of low-grade inflammation in this context.

1.1.2. In humans

Divergence in human gut microbiota composition is associated to multiple factors. Microbiota enterotypes have been defined in different populations around the world. Differentiation into these enterotypes cannot be explained by individual factors such as age or degree of corpulence, geographical location, or by dietary modifications of short duration [14]. Instead, long-term dietary habits and certain clinical characteristics seem to be stronger determinants for these compositional differences [15].

Obese and non-obese subjects have a different gut microbial profile [16–20]. Ley et al. showed that obese subjects have lower *Bacteroidetes* to *Firmicutes* ratio than lean subjects [8]. However, these findings have not been consistent in the literature [21]. Another study showed greater abundance in the *Firmicutes* group *Eubacterium rectale/Clostridium coccoides* in obese women with metabolic syndrome versus obese women with no metabolic complications and non-obese women [19]. There was a correlation between this bacterial group and certain clinical outcomes such as visceral adiposity. These findings suggest a different energy harvesting potential, consistent with the capacity of *Firmicutes* species to degrade non-digestible polysaccharides, although this remains to be proven.

An important aspect of gut microbial composition in relation to host health is microbial richness, referring to diversity in the gut ecosystem. Microbial richness is overall higher in lean vs. obese subjects, and this correlates with a healthier metabolic profile [16,22]. However even in subjects with different corpulence (lean vs. obese), metagenomic sequencing has revealed that different patterns of