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EDITORIAL

Weight loss induced by whole grain-rich diet is through a gut microbiota-independent mechanism

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Abstract

The prevalence of overweight and obesity has increased worldwide. Obesity is a well-known risk factor of type 2 diabetes mellitus and cardiovascular disease and raises public health concerns. Many dietary guidelines encourage the replacement of refined grains with whole grains (WGs) to enhance body weight management. Current evidence regarding interrelationships among WGs, body weight, and gut microbiota is limited and inconclusive. In this editorial, we comment on the article by Roager *et al* published in the recent issue of the *Gut* 2019; 68(1): 83-93. In the study, obese patients (25 < body mass index < 35 kg/m^2) were randomly assigned to receive two 8-wk dietary controlling periods with WGs and refined grain-rich diet. The results showed significantly decreased body weight in the WG group. Either the composition of gut microbiota or short-chain fatty acids, the leading end product of fermentation of non-digestible carbohydrate by gut microbiota, did not differ between the two groups. The study highly indicated that a WG-rich diet reduced body weight independent of gut microbiota. We then raised some plausible mechanisms of how WGs might influence body weight and demonstrated more literature in line with WGs enhance body weight control through a microbiota-independent pathway. Possible mechanisms include: (1) The abundant dietary fiber contents of WGs increase satiety, satiation, energy excretion from stool, and energy expenditure

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simultaneously decreasing energy absorption and fat storage; (2) The plentiful amount of polyphenols of WGs improve energy expenditure by hampering adipocyte maturation and function; (3) The sufficient magnesium and zinc of WGs guarantee lean body mass growth and decrease fat mass; (4) The effect of WGs on brown adipose tissue is a key component of non-shivering thermogenesis; and (5) The increase of adiponectin by WGs enhances glucose utilization, lipid oxidation, and energy expenditure.

Key words: Whole grain; Obesity; Microbiota; Short-chain fatty acids; Brown adipose tissue; Adiponectin

Core tip: Obesity and its co-morbidity have caused worldwide public health concerns. Many countries recommend substituting whole grain (WG) for refined grain. Roager *et al* concluded that WGs reduce body weight through a microbiota-independent pathway. We suggest that the abundant dietary fibers, the plentiful amount of minerals and polyphenols of WGs, and possible effects on brown adipose tissue and adiponectin might take part in the weight loss caused by WG diet consumption.

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INTRODUCTION

A grain has three key components – the endosperm, germ, and bran. A whole grain (WG) contains these three parts in natural proportion, while a refined grain misses at least one part[1]. The 2015 Dietary Guideline Advisory Committee viewed higher WG consumption as a healthy diet pattern and even recommended that the United States population substitute WGs for most refined grains[2]. It is widely accepted that WGs improve health outcomes such as all-cause mortality and reduce risks of life-style related diseases, including type 2 diabetes mellitus, cardiovascular disease, coronary heart diseases, and stroke[3-5]. Gut microbiota is a recently rising star candidate, as it is considered to play an essential role in the abovementioned effects[6]. Gut microbiota has also been shown to be a novel treatment target and moderator of obesity[7,8]. Some reports have suggested that increased WG consumption alters the diversity, number, or proportion of gut microbiome, further benefiting health outcomes[9-12]. However, other studies have concluded that the WG diet does not affect gut microbiota at all[13-16]. To date, evidence regarding the association among WG consumption, body weight change, and gut microbiome is not only limited but also inconclusive[17-19]. Thus we read with great interest the article by Roager *et al*[20] entitled "Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: A randomized cross-over trial" published in the *Gut* 2019, to determine whether enriched WG consumption alters body weight, and if so, if it is via the gut-microbiome-pathway.

ABOUT THE SELECTED ARTICLE

Roager *et al*[20] aimed to determine if the WG-rich diet influences the gut microbiome or body weight. They enrolled 50 non-morbidly obese patients [body mass index (BMI) between 25 and 35 kg/m^2] who received two 8-wk dietary controlling periods with a WG and refined grain-rich diet. The intake of WG was 179 ± 50 g/d and 13 ± 10 g/d during the WG and refined grain diet periods, respectively. The washout period was 6 wk between the two periods. Anthropometry, blood pressure, metabolic markers, gut permeability assessment, intestinal transit time, and urinary metabolic profiles were documented. Fecal shotgun sequencing-based metagenomics, as well as 16S rRNA amplification, were used to examine the gut microbiome. The results clearly showed a significantly decreased body weight (P < 0.001) corresponding to

enriched WG consumption. On the other hand, the composition of gut microbiome did not differ between the two groups.

Short-chain fatty acids (SCFAs) are the main end products of gut microbiota fermentation of non-digestive carbohydrates of WGs, which escape digestion and absorption in the intestines[7,21,22]. In the study, the effects of WG and refined-grain-rich diets on plasma SCFAs levels were minimal, which again support the assumption that the gut microbiota does not change much after WG diet intake, thereby indicating that weight loss induced by a WG-rich diet is through a gut microbiome-independent mechanism.

However, the authors did not directly compare the relationship between the plasma concentration of SCFAs and body weight change or inflammation markers. A weak connection between SFCAs and body weight would provide evidence that WG intake reduces body weight via a microbiome-independent pathway.

POSSIBLE MECHANISMS OF BODY WEIGHT LOSS CAUSED BY A WG DIET

If not through the microbiota, what could be the possible mechanisms of body weight loss caused by a WG-rich diet? WGs contain more dietary fibers than refined grains. Dietary fibers are classified as insoluble fibers and soluble (viscous) fibers. First, the lower digestible energy per unit mass of WGs results in lower energy intake[23]. Second, the greater size of starch particles of WGs takes more chewing effort and time, which lead to more oro-sensory stimulation and satiation[24]. Third, the large volume of fibers increases gastric distention and mechanoreceptor-mediated signals of satiation and satiety[24,25]. Fourth, soluble fibers, mostly derived from WGs, rather than from fruits or vegetables, physiologically induce the release of gut hormones secreted by enteroendocrine cells, such as peptide YY, cholecystokinin, and glucagon-like peptide-1, which are involved in glucose homeostasis and energy balance[26-29,31]. Not only the viscous fiber itself, but also the gut hormones mentioned above prolong gastrointestinal transit time and delay gastric emptying, consequently increasing satiety and inducing body weight loss[22,24,30,31]. Furthermore, fibers from WGs build up intestinal physical barriers, thus delaying absorption of glucose and fatty acid in the intestine and decreasing fat storage[22,24,25,29].

In the study by Roager *et al*[20], energy consumption in the WG group was significantly lower than that in the refined grain group. Suhr *et al*[32]. conducted a 6-wk, randomized-controlled, parallel-arm trial involving 70 non-morbidly obese patients who received a refined grain-, WG wheat-, and WG rye-based diet. Body weight decreased more in the WG rye group than in the refined grain group (-1.06 ± 1.60 and +0.15 ± 1.28 kg, respectively; $P < 0.01$). Energy consumption of the WG rye group was about 200 kcal lower than that of the refined grain group ($P < 0.05$). These results added to the evidence that the abundant dietary fibers in WGs help body weight management due to increase satiation and satiety.

Except via gut hormones, WGs might influence energy metabolism by maintenance of stool passage and increasing formation of bulkier stool[30], which lead to higher energy loss from defecation. WGs are an essential source of dietary magnesium, which helps the human body avoid constipation. In a randomized controlled study[33] including 81 healthy men and postmenopausal women divided into the WG group and refined grain group, stool characteristics including stool weight and energy, resting metabolic rate (RMR), and gut microbiota composition were examined. The diversity of microbiota did not differ between the two groups. The subjects in the WG group had significantly increased stool energy content ($P < 0.0001$) and stool weight ($P = 0.0001$). There was also a strong relationship between RMR and fiber-adjusted stool energy content. The results suggest that WGs might enhance energy expenditure by increasing stool energy excretion without altering the gut microbiome.

Very recently, Allegretti *et al*[34] performed a double-blind, randomized-controlled pilot study in 22 otherwise healthy obese patients (BMI > 35 kg/m^2), who received either capsules containing gut microbes from a lean donor or placebo. The treatment pills were found safe and able to alter the gut microbiota of the recipients. However, early results failed to show a statically significant difference in BMI and gut hormones between intervention and control groups. The above result further supports our hypothesis that the decrease of body weight and the change of gut hormones involved in appetite regulation might be independent of gut microbiota.

WGs contain more polyphenols and minerals such as iron, zinc, magnesium (Mg), selenium in comparison with refined grains[6,35]. Polyphenols interfere with the signaling pathways of adipocyte oxidation, differentiation, and proliferation, further attenuate lipogenesis, enhance lipolysis and energy expenditure[36,37]. Mg acts as a co-

factor of many metabolic reactions and a component of variable enzymes. Some rodent studies revealed that Mg deficiency reduced lean body mass and increased body fat composition[38]. The lower lean body mass caused RMR to decrease. A double-blind, randomized-controlled trial including overweight (BMI 25-30 kg/m^2) women who had taken 250 mg magnesium daily for 8 weeks demonstrated statistically significant reduction of fat mass (P = 0.02) and increase of mean lean body mass (P = 0.05) compared to the baseline measurement data[39]. Zinc depletion was shown to be related to obesity and the decline of circulation leptin levels[40,41]. Both lack of magnesium and zinc could impair the production of insulin-like growth factor-1 and growth hormone[42], therefore decrease lean body mass growth. Although human studies are scarce, it does not exclude the possibility that polyphenols and trace minerals in WGs improve body weight management.

Brown adipose tissue (BAT) is crucial in non-shivering thermogenesis, which includes both cold-induced and diet-induced thermogenesis of human energy expenditure, whereas white adipose tissue (WAT), by contrast, stores excess energy as triglycerides[43]. The stimulation of BAT is now a hot target for obesity. Xiao *et al*[44]. documented that fermented barley promoted WAT beiging and BAT activation, therefore caused body weight loss in rats. Evidence regarding the relationship between BAT and WGs in humans is still limited; more investigations are needed.

Published research suggests that WGs increase adiponectin, which is secreted by adipose tissues, and play essential roles in energy balance, fat metabolism, and glucose homeostasis[45]. It is believed that adiponectin promotes glucose utilization in skeletal muscle, suppresses glucose secretion from liver, and enhances fatty acids oxidation[46]. Additionally, adiponectin acts in hypothalamus and increases corticotrophin-releasing hormone, and further affects thermogenesis and increases energy expenditure[47]. Emerging roles of hepatokines, such as bile acids, fibroblast growth factor-19 and hepassocin, may deserve further investigation[48,49].

In short, how a WG diet affects body weight regulation is possible as, but not limited to, the following: (1) The abundant dietary fibers of WGs decrease energy intake due to the lower energy density compared with refined grain diet, attenuate bowel fat and glucose absorption, provoke satiation through stimulation of oro-sensory and gastric mechanoreceptors, enhance satiety by causing delay of gastric emptying and elongation of gastrointestinal transit time. (2) The rich content of polyphenols of WGs interfere with adipocyte signaling pathways and increase energy expenditures. (3) WGs are a good source of minerals that are key co-factors in many metabolic reactions. Sufficient Mg and zinc guarantee lean body mass growth and body fat mass decrease. (4) WGs interact with BAT, which is essential in non-shivering thermogenesis. And (5) The effect of WGs on adiponectin promotes glucose utilization, lipid oxidation, and energy expenditure.

CONCLUSION

The mechanism of how the WG-rich diet influences body weight is still ambiguous. Here we suggest that the ability of WGs to decrease body weight is, at least in part, related to multiple microbiota-independent pathways. We summarized the hypothetic pathways in Table 1. Further studies should thoroughly examine if different types of WGs, such as wheat, brown rice, millet, maize, barley, rye, oats, triticale, various population subgroups, the different amount of WG consumption, and different duration of intervention act on the relationship among WG diet, body weight, and gut microbiota. Standardized protocols and new biomarkers regarding changes in the species, diversity, and function of fecal microbiota are in need. Furthermore, more investigations should aim at whether the WG diet improves body weight regulation through the alternation of RMR, gut hormones associated with satiety, BAT, and adiponectin in the future.

Table 1 Possible mechanisms of whole grain diet affect body weight regulation

Mediator	Mechanism
Dietary fibers in WGs	Lower energy density results in less energy intake
	Attenuation of intestinal nutrition absorption
	Stimulation of oro-sensory and gastric mechanoreceptors result in increased satiation
	Delay of gastric emptying and gastrointestinal transition result in increased satiety
Polyphenols in WGs	Interferes with adipocyte signaling pathways results in more energy expenditures
Minerals in WGs	Magnesium and zinc are co-factors in lean body mass growth and body fat mass decrease
Brown adipose tissue	Non-shivering thermogenesis
Adiponectin	Promotes glucose utilization, lipid oxidation, and energy expenditure

WGs: Whole grains.

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