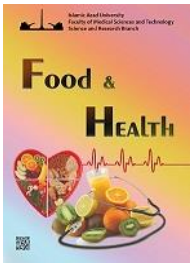

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Effect of low-FODMAP diet on gastrointestinal symptoms in patients with irritable bowel syndrome: A systematic review of randomized controlled trials

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ABSTRACT

Irritable bowel syndrome is the most common gastrointestinal functional disorder accompanied by symptoms such as abdominal pain and changes in intestinal habits. Lack of proper biochemical criteria for diagnosis, as well as a lack of proper understanding of the pathophysiology of this disease, complicates diagnosis of this disease and undermines the serious efforts to discover the proper drug for it. The present treatments including medical treatments which are related to some side-effects such as dyspepsia, heartburn, headache, bradycardia, anorexia, weakness and fatigue and diet therapy. The aim of this study was to summarize the results of previous studies on the effect of low-FODMAP diet on the improvement of digestive symptoms and nutritional status in patients with IBS. Electronic literature searches were conducted on PubMed, Web of Science and Google Scholar until May 2019. The search was conducted with the following words “FODMAP” or “low-FODMAP diets”, in combination with “gastrointestinal symptoms”, “diarrhea”, “constipation”, “dyspepsia”, “bloating”, “burp”, “heart burn”, “nausea” and “intestinal cramp” among randomized clinical trials. Our search was supplemented with the search of publisher databases Elsevier, Wiley Online and SpringerLink and for any pertinent studies, we screened the references of all included studies. Eligibility criteria included: randomized controlled clinical trial studies published in peer-reviewed journals and studies that used low-FODMAP diets as an intervention. In the total of 5 studies were done on the 299 adults who meet the inclusion criteria. According to the consumption of the results, the low-FODMAP diet caused a significant improvement in many gastrointestinal symptoms, such as abdominal pain, bloating, diarrhea, constipation, and dissatisfaction of the intestinal habits in comparison with control diet. According to the results of various studies, it seems that a low-FODMAP diet can improve digestive symptoms and IBS-related complaints.

1. Introduction

Irritable bowel syndrome (IBS) is a common digestive functional disorder, which is characterized by symptoms such as abdominal pain, bloating, and changes in intestinal function without any damage to the tissue. The role of diet in triggering IBS symptoms has long been recognized (1). One billion people, or 15% of the world's population are affected by this disease (2). IBS also affects an average of 11% of the adult population in developing countries (1). In Iran, the prevalence of IBS is between 1.1 to 25 percent and it is more common in women than men (3). It is estimated that there will be an annual total cost of 2.8 million $ for an urban adult population, which is a heavy burden on Iran's economy as a developing country (4, 5). Moreover, a study by the American Gastroenterology Association (AGA) in 2015 reported that symptoms of patients with IBS reduce their labor productivity by 9 days a month on average and these patients also lose two business days. For this reason, the indirect costs of this disease are estimated to 20 billion $ in the United States and per capita cost per patient is estimated to be 9933 $ in 2012 (6). In addition, IBS affects 10% to 15% of adults in the United States and results in significant disorders in health-related quality of life (HRQOL), daily work and labor productivity as well as

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indirect costs (6). Current treatments including pharmacological interventions, diet therapy, and behavioral treatments. The following drug categories are used to treat IBS: anti-depressants, mint oil, non-absorbable antibiotics from the intestines and the drugs which stimulants GABA secretion (7). Antidepressants normally prevent reabsorption of certain neurotransmitters such as norepinephrine and serotonin and dopamine in nerve terminals which despite promising results, there are significant side effects such as anxiety and mental disorders as well as gastrointestinal, genital organs, eating disorders and pain (8). The most reliable evidences support drugs such as rifaximin, lubiprostone, fiber supplement and mint oil for treatment of IBS. New drugs for IBS treatment are μ receptor agonists and opioid antagonists δ (9). Considering the significant side effects of the mentioned drugs, dietary approaches with fewer side effects are also desirable. Among the diets reviewed in this case, diets with limited FODMAPs like short chain carbohydrates such as lactose, fructose, galactoalogosaccharides (such as fructan and galactones) and Polysaccharide alcohols (such as sorbitol and mannitol) are recommended (10). FODMAPs are simple carbohydrates that are not absorbed in the small intestine but also are fermented with high speed in the ascending colon. Recent clinical studies show a possible positive effect of the low-FODMAP diet in IBS (1). However, FODMAPs are one of the most important gastrointestinal stimulants. For example, recent studies of people undergoing ileostomy indicate that a diet with high-FODMAPs can lead to changes in liquids volume and production of CO_2 and H_2 from the fermentation in the proximal region of intestine (2), which can ultimately stimulate bowel gas production, abnormal bowel movements, visceral sensitivity, increasing the rate of fermentation and causing IBS symptoms. Considering the large number of people in the world with IBS and the lack of complete therapies for treating patients and improving their quality of life, new treatments need to be studied and evaluated. The aim of this study was to summarize the results of clinical trials conducted to evaluate the effect of low-FODMAP diet on the reduction of IBS symptoms.

2. Methods

Electronic literature searches were conducted on PubMed, Web of Science and Google Scholar until May 2019. Our search was supplemented with the search of publisher databases Elsevier, Wiley Online and SpringerLink and for any pertinent studies, we screened the references of all included studies. There were no restrictions regarding the language of publications. The search was conducted with the following words “FODMAP” or “low-FODMAP diets”, in combination with “Gastrointestinal Symptoms”, “Diarrhea”, “constipation”, “dyspepsia”, “bloating”, “burp”, “heart burn”, “nausea” and “intestinal cramp” among randomized clinical trials. Eligibility criteria included: randomized controlled clinical trial studies published in peer-reviewed journals and studies that used low-FODMAP diets as an intervention. Duplicates were removed (8 articles); the relevant papers were selected in three phases. In the first and second phases, titles and abstracts of papers were screened and irrelevant papers were excluded. In the last phase, the full text of recruited papers was explored intensely to select only relevant papers. After excluding the studies that did not report our primary outcome or fit the criteria, six suitable studies were identified for review (Fig. 1). Our primary outcomes were gastrointestinal symptoms of IBS.

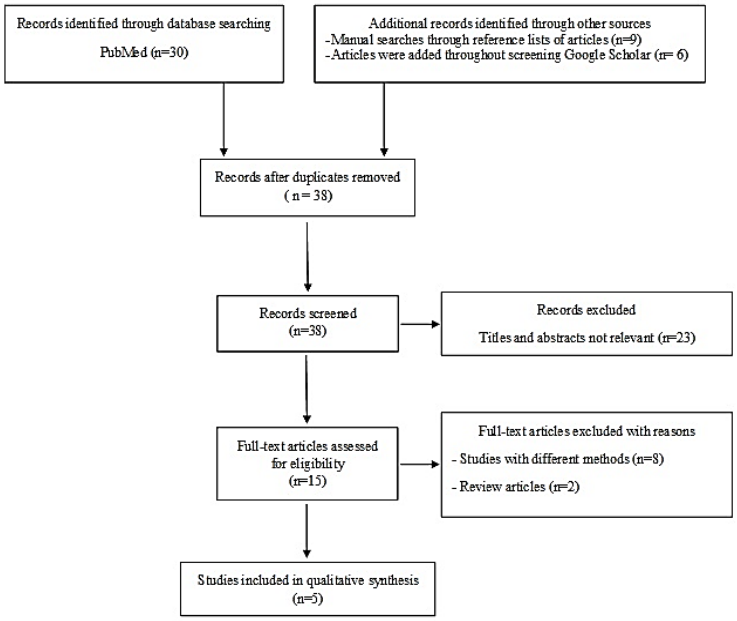

Fig. 1. Study flow diagram showing the selection process of articles eligible for review.

3. Results

Investigating the studies conducted in this area showed five studies have examined the effect of low-FODMAP diet on IBS. The minimum number of subjects was 30 (2), and the maximum number was 84 (11). A total of 299 people have been studied in these articles. The investigated factors including abdominal pain and bloating (In three studies) diarrhea, gas passage, heartburn, hydrogen level of breathing (in two studies), nausea, burp, intestinal cramp, dyspepsia, defective disposal, emergency excursion, change in percentage of kings stool score, dissatisfaction with stool tissue, stool strength, frequent disposal, abdominal distension, abdominal pain alternation, severe abdominal pain, dissatisfaction with the intestinal habit, interactions in daily life, fatigue, blood lipid profiles, inflammatory factors and methane levels of respiration. (Table 1).

3.1. Abdominal pain

Of the three studies that examined the effect of low-FODMAP diet on abdominal pain, they all showed positive effects. In the study of Ong et al. (2) the abdominal pain score was significantly lower in subjects with a low-FODMAP diet compared to those who had a high-FODMAP diet (p=0.006).

However, the score for abdominal pain in healthy subjects using the high-FODMAP diet did not differ significantly from those who used the low-FODMAP diet (p=0.145). In the study of Laatickainen et al. (1), the abdominal pain score in people with IBS was significantly lower when they were using the low-FODMAP diet compared with when they were using the high-FODMAP diet (p=0.039). The average difference of scores was 5 (0-9). In the study of Halmos et al. (12), the abdominal pain in IBS group was significantly improved in those who used the low-FODMAP diet in comparison with those who used normal diet (p<0.001) and in the control group there was no difference Between two diets in the severity of symptoms.

3.2. Bloating

In the three studies mentioned above, assessing the effect of a low-FODMAP diet on bloating, they all found positive effects. In the study of Ong et al. (2) which was conducted on people with IBS, the score for bloating was significantly lower when they were using low-FODMAP diet compared to when they were using high-FODMAP diet (p=0.002). However, the score for bloating in healthy subjects showed no significant difference whether they used the diet with low-FODMAP or high-FODMAP (p=0.484). In the study of Halmos et al. (12), bloating was significantly better in subjects with low-FODMAP diet than those who had a normal diet (p<0.001). There was no evidence about the difference in the severity of the symptoms between two diets in the control group. In fact, there was no change between general and individual symptoms and there was an improvement in gastrointestinal symptoms in 70% of subjects. Therefore, having a low-FODMAP diet was effective in comparison with the control group in this study. In the study of Laatikainen (1), bloating was higher in people with IBS when taking a high-FODMAP diet compared to a normal FODMAP diet. The average of differences in scores was 4 (0-8). In two studies on diarrhea, the positive effect of the low-FODMAP diet was expressed.

3.3. Diarrhea

In two studies that examined the effect of low-FODMAP diet on diarrhea, they all expressed positive effects. In the study of Laatikainen et al. (1), the score of diarrhea in people with IBS was higher when taking a high-FODMAP diet compared to a normal FODMAP diet. The difference in scores was 2 (2-7). In the study of Yoon et al. (11), diarrhea had a significant improvement in the group consuming a low-FODMAP diet compared to those with moderate or high FODMAP diets. This pattern was found in both subgroups of diarrhea and constipation, and in the subgroup of only suffering from diarrhea. Improvement of diarrhea in a group

Table 1. Characteristics of included studies.

Study	Number of participants	Study design	Blinding	Randomization	Results
Laatikainen et al. (1)	73	Crossover clinical trial	Double blinded	Randomized	- Abdominal pain was reduced (p=0.0049). - Diarrhea was improved (p=0.31). - Constipation was not significantly difference (p=0.66). - Bloating was significantly lower (p=0.004). - Heartburn was significantly lower. (p=0.034). - Intestinal cramp was significantly lower (p=0.01). - Dyspepsia didn't have any significantly difference (p=0.06). - Defective Excretion was not significantly different. (p=0.066). - Necessity in excretion was not significantly different (p=0.011). - Hydrogen level of breathing was significantly lower (p=0.01)
Yoon et al. (11)	84	Crossover clinical trial	Double blinded	Randomized	- Diarrhea and percentage of changes in the score of excretion had a significant improvement (p<0.05). - Weight showed no significant difference. - Serum albumin level increased significantly (p<0.01).
Böhn et al. (13)	67	Clinical trial	Single Blinded	Randomized	- Severity of abdominal pain didn't have significant difference (p=0.6). - Abdominal pain alternation was significantly reduced (p<0.008). - Abdominal distension was reduced (p<0.001). - Fecal strength did not differ significantly (p=0.12). - Frequent fecal was improved (p=0.001). - Dissatisfaction with intestinal habit had no significant difference (p=0.22). - Interacting with everyday life was improved (p=0.001).
Halmos et al. (12)	38	Crossover clinical trial	Single Blinded	Randomized	- Abdominal pain was reduced (p=0.001). - Bloating was significantly lower (p<0.001). - Dissatisfaction with fecal strength was reduced (p=0.001).
Ong et al. (2)	30	Crossover clinical trial	Single Blinded	Randomized	- Abdominal pain was significantly lower (p=0.006). - Bloating was significantly lower (p=0.002). - Nausea was significantly lower (p=0.01). - Heartburn was reduced (p=0.025). - Passing too much gas was significantly lower (p=0.002). - Fatigue and drowsiness were also significantly lower (p=0.012).

with diarrhea and constipation, which included two subgroups of drug consumers and those who did not take the drug, were 73.3% (p=0.46), and 71.4% (p=0.028), respectively. In the subgroup of only suffering from diarrhea which included two subgroups of drug consumers and those who did not take the drug, were 60% (p=0.047) and 90% (p=0.035), respectively.

3.4. Nausea

A study reported the positive effect of the low-FODMAP diet on nausea. In the study of Ong et al. (2), nausea score in healthy subjects who use low-FODMAP diet, did not have a significant difference compared with those who had high-FODMAP diet (p=0.007) and the score for nausea in people with IBS who used low-FODMAP diet was significantly lower than those who used high-FODMAP diet (p=0.01).

3.5. Heartburn

Two studies examined the effect of low-FODMAP diet on heartburn, one of them found a significant difference and the other one did not find any significant difference. In the study of Ong et al. (2), the score for heartburn in healthy subjects who had a low-FODMAP diet did not have any significant difference from those who had a high-FODMAP diet (p=0.424). Heartburn was significantly lower in people with IBS who used low-FODMAP diet than who had a high-FODMAP diet (p=0.025). In the study of Laatikainen et al. (1), the score for heartburn in people with IBS who had used the low-FODMAP diet did not have any significant difference compared to when they used a normal diet. The average difference of scores was 2 (2-5) (p=0.34).

3.6. Constipation

The only study which evaluated the effect of low-FODMAP diet on constipation did not express any positive effect. In the study of Laatikainen et al. (1), in subjects with IBS, there was not significantly difference when taking low-FODMAP diet compared to when they used a normal diet. The average difference of scores was 1 (3-5) (p=0.66).

3.7. Hydrogen level of breathing

In the study of Laatikainen et al. (1), the hydrogen level of breathing was 52.9 ppm/min after consuming a low-FODMAP diet and was 72.6 ppm /min after having a normal diet. That means the hydrogen level of breathing was significantly lower after taking low-FODMAP diet (p=0.01). In the study of Ong et al. (2), the hydrogen level of breathing in both healthy and patient subjects was significantly higher after taking high-FODMAP diet p<0.0001). Also, people with IBS significantly produced more hydrogen than healthy subjects who used high-FODMAP or low-FODMAP diet. (p=0.039) in HFD5 and (p=0.025) in LFD6 (2).

3.8. Fatigue and drowsiness

In the study of Ong et al. (2), fatigue and drowsiness score did not have any significant difference in healthy subjects who used low-FODMAP diet compared to those who used high-FODMAP diet (p=0.454). Fatigue and drowsiness were also significantly lower in the group with IBS who used low-FODMAP diet, in comparison with those who used high-FODMAP diet (p=0.012).

3.9. Passing too much gas

In the study of Ong et al. (2), the score of passing too much gas was lower in healthy subjects who consumed low-FODMAP diet than those using high FODMAP diet (p=0.007), and in the group with IBS who used low FODMAP diet, passing too much gas was significantly lower than those who used high-FODMAP diet (p=0.002).

3.10. Gas passing

In the study of Halmos et al. (12), the gas passing score in people with IBS who used a low-FODMAP diet was significantly lower than those who used high-FODMAP diet.

3.11. Intestinal cramp

In the study of Laatikainen et al. (1), the intestinal cramp score was significantly lower in subjects who had a low FODMAP diet compared to those who received normal diet (p=0.01). The average difference of scores was 6 (2-10).

3.12. Burp

In the study of Laatikainen et al. (1), the burp's score was significantly lower in subjects with the low FODMAP diet compared to those receiving normal diets (p=0.001) and the average difference of scores was 6 (3-10).

3.13. Dyspepsia

In the study of Laatikainen et al. (1), the score of dyspepsia didn’t have any significant difference in people who had a low FODMAP diet compared to those who received a normal diet (p=0.06) and the average difference of scores was 4 (0-8).

3.14. Defective Excretion

In the study of Laatikainen et al. (1), the defective excretion's score in subjects with a low-FODMAP diet was not significantly different from those who used the normal diet (p=0.66), and the average difference of scores was 1 (3-5).

3.15. Necessity of Excretion

In the study by Laatikainen et al. (1), the score for the necessity of excretion was not significantly different in subjects with low-FODMAP diet than those who used normal diet (p=0.11) and the average difference of scores was 4 (1-8).

3.16. Fecal strength dissatisfaction

In the study by Halmos et al. (12), the score of fecal strength dissatisfaction in the IBS group with low-FODMAP diet was significantly lower than those who used normal diet (p=0.001) and in the control group there was no significant difference in, the severity of symptoms between two groups that one of them had low-FODMAP diet and one had normal FODMAP diet (p=0.304).

3.17. Fecal strength

In the study by Bohn et al. (13), the fecal strength in both of IBS groups with low-FODMAP diet and the group using traditional IBS diet did not differ significantly between baseline and post-intervention (p=0.12 and p=0.7, respectively).

3.18. Frequent fecal excretion

In the study of Bohn et al. (13), the frequent fecal excretion in patients with IBS who used low-FODMAP diet improved from baseline (p=0.001) and in IBS group using traditional IBS diet, there was no significant difference in baseline compared to intervention (p=0.15).

3.19. Percentage of changes in fecal scores KINGS

In the study of Yoon et al. (11), the percentage of changes in fecal scores Kings was significantly decreased in those using low-FODMAP diet in comparison with those having a high or a moderate FODMAP diet. That was seen in both groups with diarrhea and constipation and in a group with diarrhea only (p<0.05 for everyone).

3.20. Dissatisfaction from intestinal habit

In the study of Bohn et al. (13), dissatisfaction from intestinal habit in both IBS group who used low-FODMAP diet and group using traditional IBS diet had no significant difference after the intervention than base mode (p=0.22 and p=0.47, respectively).

3.21. Severity of abdominal pain

In the study by Bohn et al. (13) on IBS group with low-FODMAP diet, there was no significant difference after the intervention than baseline. Also, there was no significant difference in the IBS group used traditional IBS diet after the intervention compared to baseline (p=0.6).

3.22. Frequency of abdominal pain

In the study by Bohn et al. (13) in both IBS groups with low FODMAP diet and group used traditional IBS diet, Frequent abdominal pain was improved after intervention in comparison with baseline. (p<0.008 and p<0.001, respectively).

3.23. Extension of the abdomen

In the study by Bohn et al. (13) extension of the abdomen was improved after the intervention in both IBS groups with low-FODMAP diet and group used traditional IBS diet compared to baseline (p<0.001 and p=0.003, respectively).

3.24. Interference with everyday life

In the study by Bohn et al. (13) in both IBS groups with low-FODMAP diet and traditional IBS diet group improvement was seen after the intervention compared to baseline (p=0.001 and p=0.002, respectively).

3.25. Weight

In the study by Laatikainen et al. (1) weight differences in patients before and after the intervention was significantly lower in the intervention group compared with control patients (p=0.03, 0.5 kg). In the study of Yoon et al. (11) weight of patients before and after the intervention was not significantly different in three groups who consumed high, low or moderate FODMAP diet.

3.26. Total serum albumin concentration

In a study by Yoon et al. (11) total serum albumin in three groups that used high, moderate or low-FODMAP diets increased significantly after the intervention compared to the baseline (moderate FODMAP diet p<0.05 and high or low-FODMAP diet p<0.01). No side-effect was mentioned in any of the studies.

4. Discussion

In previous years, along with drug therapies to control the symptoms of IBS, the use of low-FODMAP diet has been studied in several studies. A low-FODMAP diet reduces symptoms such as abdominal pain, bloating, intestinal cramp, fermentation in clone, vomiting, abdominal pain, abdominal noise in comparison with a normal diet, and reduces the total score in all IBS subtypes (1, 2, 12, 13). Patients with IBS who took low-FODMAP diet showed more decrement in their gastrointestinal symptoms including diarrhea in comparison with those with high or moderate FODMAP diet. Reducing diarrhea also improves the nutritional status and faster recovery of patients with IBS and IBD (11). Low-FODMAP also diet reduces dissatisfaction rates of fecal consistency and KSC scores, which are related to the molecular size and osmotic properties of FODMAP. In addition, serum levels of total albumin, which is a short-term nutritional marker, has been recovered quickly in IBS patients who used low-FODMAP diets compared to other groups (11, 12). A low-FODMAP diet in patients with IBS reduces the volume of intestinal contents and hydrogen production, also reducing the accumulation of gas in the clone and the production of methane in healthy people (1, 2). A low-FODMAP diet

reduces 70% of symptoms in all four types of IBS. These results indicate that diet with low level of FODMAPs is effective in most patients with IBS (12). Ong et al. (2) also found that heartburn had been lowered when using lower-dose of FODMAP diet compared to high-FODMAP diet, but in the study of Laatikainen et al. (1) Heartburn did not show to have any significant difference between having low-FODMAP diet and normal diet. Weight of patients in the study of Laatikainen et al. (1) was significantly lower than the end of the intervention, and in the study of Yoon et al. (11), there was no significant difference in patients' weight after intervention in three groups given high, low or moderate FODMAP diet. Low-FODMAP diet reduces total gastrointestinal gases in clone by reducing the level of FODMAP fermentation and also in healthy people reduces the volume of luminal gas and relative change in the production of methane by changing the functional capabilities of methanogens (methane-producing bacteria) (1, 2). Low-FODMAP diet in people with IBS results in less water retention in the lumen of the intestine and less gas production in the intestine than in high or moderate FODMAP diet, thereby reduces digestive symptoms especially diarrhea which is related to molecular size and osmotic properties of FODMAPs (11). Diet with low-FODMAPs reduces the transport time and severity of constipation in people with IBS who have constipated constipation or are at risk of constipation (2). A high-FODMAP diet causes gastrointestinal symptoms. For example, fructans as heterogeneous groups of linear or branched fructooligosaccharides, due to the lack of enzymes that hydrolyzing β (1→2) links, are not absorbed in the small intestine so they are accessible to clone's fermentative bacteria and produce gas (14-16). A diet with low-FODMAP without galactooligosaccharide and sorbitol, because of lacking of α-galactooligosaccharide in mammals, which is not digested in diet and come to clone and produces gas by fermentative bacteria (17, 18). Low-FODMAP diet inhibits fructan and GOS and are based on probiotic foods and have an indirect effect on immunity performed by stimulating the gastrointestinal modulating bacteria such as *Bifidobaceria* and *Faecalibacterium* (19-22). Also, diet with low-FODMAPs affects the reactions between receptors with diagnostic patterns on the cover and immunity intestinal cells and improves the immune system directly (16). According to the fund meta-analysis by World Cancer Research Center, the prevalence of colorectal cancer is rising in many countries and it is assumed that one of the mechanisms cause this disease is the fermentation of non-absorbable protein in the large intestine which is created by red and processed meat. In this case, the low-FODMAP diet boosts water and also reduces the fermentation of non-absorbable proteins in the clone of patients with IBS, which means that restriction of FODMAPs may have a beneficial effect on the prevention of colorectal cancer. However, this needs to be further investigated in specific clinical trials. Laatikainen et al. (1) study was one of the rare and stunning studies in the concept of FODMAP which used elaborated study design. However, in the study by Bohn et al. (13), a single-blinded method was used. One of the weaknesses in the study of Bohn et al was the presence of more oligo-saccharide and poly-ethyl content in the normal diet than baseline, which caused more symptoms in people with IBS using normal diet than base diet. Low adherence of participants was another weakness of this study because some of the participants did not use the diet because of intolerable symptoms.

5. Conclusion

Data from the investigated studies showed that low-FODMAP diets might have some positive effects on the treatment of functional gastrointestinal symptoms and diarrhea. FODMAP diets might also be able to improve nutritional status and accelerate the recovery process from illness. The low-FODMAP diet also resulted in a lower fermentation level in the colon, less flatulence, less abdominal pain, fewer cramps, and less stomach rumbling.

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