

Bowel movement frequency, oxidative stress and disease prevention (Review)

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Abstract. The significance of diet for disease prevention has long been recognised. Dietary recommendations have therefore been integrated in health promotion messages. Gastrointestinal functioning is essential for the digestion of nutrients. Oxidative stress has been observed in patients with constipation, as well as in those with colorectal cancer, cardiovascular disease and other chronic illnesses associated with constipation. The coexistence of colorectal neoplasia and coronary artery disease has been incriminated for exposure to common risk factors associated with increased oxidative stress. It was recently demonstrated that bowel movement frequency is inversely associated with cardiovascular mortality. The aim of the present study was to review the relevant literature in light of these findings. It was concluded that suboptimal functioning of the large bowel may contribute to oxidative stress and, therefore, to increased mortality. Bowel movement frequency may represent a simple quantifiable indicator of adequate colonic function and it is dependent on diet, exercise and other lifestyle factors, but also on individual characteristics, including colonic microbiota. Future health promotion actions may improve the prevention of a number of diseases by advocating lifestyle personalisation for assuring optimal intestinal functioning.

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1. Introduction

Dietary habits significantly affect the incidence of colorectal cancer, cardiovascular disease and other chronic illnesses. The high prevalence of colonic polyps among patients hospitalized for coronary artery disease is considered to be due to shared underlying risk factors, i.e., old age, male gender, diabetes, hyperlipidemia, smoking history and high body mass index (1). All these risk factors have been associated with increased oxidative stress. Solid evidence has been obtained regarding the nature of diets preventing cardiovascular events (2). A comparison of the Mediterranean diet and less well-known diets, also associated with a decreased risk of cardiovascular events, revealed several shared characteristics: High intake of unrefined carbohydrates, moderate protein intake with emphasis on vegetables/legumes, fish and lean meats as the sources, and a healthy fat profile, higher in mono/polyunsaturated fats, lower in saturated fat and rich in omega-3 fatty acids (3). These diets are plant-rich, suggesting that fibres and resistant starch play important roles (4,5). All diets result in a low glycemic load, less oxidative stress and less inflammation (3). The impact of these dietary characteristics on public health is already important regarding prevention of cardiovascular disease. Adherence to the Mediterranean diet reduces cardiovascular events to a degree greater than low-fat diets and, importantly, equal to or greater than the benefit observed in statin trials (6). Dietary recommendations for disease prevention have therefore been integrated in health promotion messages.

As diet is important for disease prevention, so is intact gastrointestinal function. The mechanisms controlling gastrointestinal function are numerous and complex. Simple quantifiable indicators of adequate function associated with prevention of chronic diseases were not previously available. However, the recently published 13-year study of Honkura *et al* provides evidence supporting an association of self-reported defecation frequency with cardiovascular mortality (7). Integrating the significance of daily bowel movements in health promotion messages may therefore be in the public interest.

2. Rationale

Since the 1970s it has been suggested that dietary fibre may help prevent colorectal cancer and cardiovascular disease by

affecting the bacterial flora and physiological processes in the gut (8). An increased fibre intake shortens the oro-cecal transit time, which was considered to affect the risk for colorectal cancer and cardiovascular disease, as well as other diseases (8). A meta-analysis of risk factors for colorectal cancer in China identified dietary fibre intake as protective (9). A recent systematic review and meta-analysis confirmed that an increased intake of total dietary fibre is associated with a lower risk of cardiovascular disease in healthy populations (4). Dietary modifications affect the number and types of gut bacteria and their metabolic activity (10). However, individuals with identical dietary intakes may exhibit a threefold difference in transit times (11).

Further research was therefore focused on the effect of pharmacologically manipulating the transit time on energy production in the colon with equal dietary intake (12,13). Slowing down transit reduced the fermentation efficacy of complex carbohydrates and led to a diminished production of the short-chain fatty acids (SCFAs), acetic acid, propionic acid and butyric acid, of which butyric acid is an energy source for colonocytes and for the host. However, accelerating transit increased energy production (12). Approximately twice as much butyric acid was produced in the fast-transit compared with that in the slow-transit group. The ratio between acetic acid and propionic acid was also roughly two times higher in the slow-transit group. Decreasing the acetate/propionate ratio may reduce serum lipids and, therefore, possibly cardiovascular disease risk (14). Individual differences in the molar ratios and concentrations of acetate and propionate and concentrations of butyrate in the feces were reported to remain constant, at least over a period of >3 years (15).

Severe constipation, often accompanied by slower transit, was found to be associated with cardiovascular risk, at least in post-menopausal women (16). The association of constipation with colorectal cancer is controversial (17,18). However, a recent study involving ~29,000 patients with chronic constipation and >86,000 controls reported that chronic constipation is associated with a significantly higher prevalence and incidence of colorectal cancer and benign colorectal neoplasms compared with those in matched chronic constipation-free individuals. These risks increase with the severity of chronic constipation (19). Chronic constipation is caused by a variety of factors (20); however, it is difficult to quantify and, therefore, less convenient as an indicator of cancer or cardiovascular risk. The data of Honkura *et al* (7) demonstrated that bowel movement frequency may be a promising indicator for public health purposes. It is therefore relevant to reflect on the mechanism(s) underlying the association of defecation frequency with disease risk.

Butyrate provides energy for colonocytes. Colonising germ-free animals with gut bacteria allows the animals to harvest otherwise inaccessible nutrients (21). As a result, the NADH/NAD⁺ ratio and the ATP levels in their colon increase (22). Energy deficiency in colonocytes leads to a decrease in cellular oxidative phosphorylation, with oxidative stress as a result (23). In an attempt to maintain energy homeostasis, 5'-adenosine monophosphate-activated protein kinase, a sensor that is activated by decreasing ATP levels (24), induces autophagy in the colonocytes (22). Butyrate, following beta oxidation to acetyl-CoA, enters the tricarboxylic acid

cycle. This leads to the reduction of NAD⁺ to NADH, which enters the electron transport chain, resulting in the formation of ATP and CO₂ (22) and diminishing autophagy and oxidative stress.

The fecal stream is crucial for the integrity of the colonic mucosa. Following surgical diversion of part of the intestine, luminal concentrations of SCFAs are significantly reduced in the bypassed part of the intestine (25). Colonic segments without a fecal stream exhibit high levels of oxidative DNA damage, which increases with the time of intestinal exclusion (26). Enemas with the antioxidant N-acetylcysteine significantly reduce oxidative DNA damage in colonic segments without a fecal stream (27). Dietary resistant starch increased SCFAs and reduced inflammation and cell proliferation in a rat colitis-associated colorectal cancer model (28). The SCFAs may represent only one of the factors involved in reducing oxidative stress. The Mediterranean diet contains more macromolecular antioxidants compared with the low-molecular weight or soluble antioxidants usually taken into account (29). Macromolecular antioxidants are only released during the process of colonic fermentation (30); they may also reduce oxidative stress and they play a role in maintaining the luminal reductive environment, protecting the growth of anaerobic microbiota (31).

Several mechanisms have been proposed above to explain how accelerating transit and avoiding constipation reduces oxidative stress. However, it remains unclear whether the cumulative effect is of a sufficient magnitude to prevent cardiovascular disease. Chronic kidney disease is characterized by oxidative stress and increased incidence of cardiovascular mortality (32,33). In a rat model of chronic kidney disease, a high amylose-resistant starch diet was shown to ameliorate oxidative stress, inflammation and progression of chronic kidney disease (34). The Mediterranean plant-rich diet favours the prevalence of saccharolytic species among gut microbiota, whereas the Western meat-rich diet promotes a shift towards a proteolytic profile, causing dysbiosis (35). The gut microbiota thus forms a plausible link between adherence to the Mediterranean diet, reduced oxidative stress and decreased loss of kidney function (35,36). Oxidative stress plays a role in the etiopathogenesis of several diseases associated with constipation (37). Oxidative stress leads to intestinal dysmotility, creating a vicious cycle (38,39). The intestinal microbiota may therefore have the potential to significantly affect oxidative stress and the progression of all the constipation-associated diseases in the host. Two independent population-based studies reported that chronic constipation is associated with increased mortality (40,41). The key issue is whether the alleviation of constipation reduces oxidative stress and the risk for the associated diseases; there is evidence that this may be the case (37). In an animal model, inducing constipation led to oxidative stress, whereas prebiotics attenuated both constipation and oxidative stress (42). Prolonged duration of constipation in children was found to lead to oxidative stress (43) and growth retardation (44), whereas effective management of constipation attenuated the growth retardation (44). Consequently, assuring proper bowel movement frequency may significantly affect public health.

Surprisingly, defecation frequency was only poorly correlated with whole-gut and colonic transit times (45,46). A more

regular fecal flow associated with more frequent bowel movements may, besides the transit pace, be an additional factor increasing the efficacy of the fermentation process and its effect on oxidative stress. This is a plausible hypothesis, but remains to be confirmed in future studies. In this context, it may be of interest to include defecation frequency as a parameter, independent of solids retention time, in a recent *in silico* model of colonic fermentation (47).

3. Conclusion

Several chronic diseases, including certain types of cancer, metabolic syndrome and diabetes, share common behavioural risk factors with colorectal cancer and cardiovascular disease. These include: Active and passive smoking, being overweight, a sedentary lifestyle, an unhealthy diet and more than occasional alcohol consumption. Oxidative stress plays a role in the etiopathogenesis of these diseases and is associated with the abovementioned behavioural risk factors. The global epidemic of cardiovascular and other chronic diseases is still evolving, including in China (48). A number of organizations focused on these chronic diseases aim at jointly supporting approaches for the reduction of shared risk factors, while at the same time retaining disease-specific programs (49). Once the results of Honkura *et al* (7) are independently confirmed, global actors for this set of diseases may maximize their efforts by integrating the significance of daily bowel movements into future concerted health promotion messages and actions. This could be vital for success of disease prevention and reduction of mortality.

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