Peritoneal Dialysis International, Vol. 35, pp. 650–654
www.PDIConnect.com

0896-8608/15 $3.00 + .00

THE GUT IN OLDER PATIENTS ON PERITONEAL DIALYSIS

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Age-related changes in gastrointestinal symptoms need to be considered in peritoneal dialysis (PD) patients. A diminishing appetite is associated with aging and may be exacerbated by renal failure and PD treatment, meaning that attention to dietary adequacy is important in the older patient. Constipation and its treatment may increase the risk of peritonitis, but is important for comfort as well as trouble-free dialysis. Diverticulosis increases with age, and whilst there may be ethnic differences in the patterns of this condition, there is conflicting evidence regarding the risks of peritonitis associated with asymptomatic disease. Hernias, urinary incontinence, and prolapse are also common and made worse by PD, so it is important to know about these issues prior to starting. Whilst data around these topics are scant and some studies conflicting, further understanding these issues and considering mitigation strategies may improve technique survival and quality of life.

***Perit Dial Int* 2015; 35(6):650–654**
http://dx.doi.org/10.3747/pdi.2014.00341

KEY WORDS: Peritoneal dialysis; gut; constipation; appetite; diverticular disease.

The proximity of the peritoneal membrane used for peritoneal dialysis (PD) to the gut means that consideration of gut function is important in technique success. Not only does a well-functioning bowel improve comfort for PD patients, it is important when considering nutritional adequacy, and this is directly linked to patient survival. We consider a number of factors related to gut function and the interaction with this dialysis technique, especially important in the older patient.

APPETITE AND MALNUTRITION IN THE OLDER PD PATIENT

A reduced appetite is a common symptom of aging (1) that may parallel renal dysfunction (2), often leading to protein-energy wasting. Thus, anorexia diminishes dietary protein and calorie intake, which, combined with protein loss in the dialysate effluent (3), can result in lower albumin levels, and these predict mortality (2,4). Whilst the anorexia of renal failure often partially recovers with dialysis, PD patients do seem to have a lower desire for food than those on HD (5), and the recognition of this issue, dietetic intervention, and on-going monitoring are important. Patients on PD have been reported to have more gastrointestinal (GI) symptoms (including nausea, vomiting, bloating, early satiety, anorexia, and heartburn) compared with those on HD, further contributing to reduced appetite (6). However, the reasons for this are not straightforward, and whilst mechanical pressure on the stomach and higher intra-abdominal pressures may play a part, a number of hormonal factors may be etiologically important. In small studies, gastric emptying takes longer in most PD patients when full than when empty (7,8).

Leptin is an appetite-suppressing hormone produced by adipose tissue, and serum levels are higher in PD patients than in healthy controls. The mild hyper-insulinemia resulting from dialysate glucose uptake can also enhance leptin production (9). In addition, levels of the hormone ghrelin decline in older subjects. This hormone is released during fasting and increases appetite and meal size and induces fat and weight gain. Ghrelin levels are lower in PD patients in association with an increase in body fat mass, compared with hemodialysis (HD) patients (10). In 1 study, the subcutaneous administration of ghrelin to PD patients resulted in a sustained increase in caloric intake (11), and bicarbonate-buffered solutions were associated with higher ghrelin levels in another study (12). The effects of dialysate glucose have not been shown to affect dietary intake in humans (13), although in animal studies, lower glucose concentrations and bicarbonate-buffered PD solutions have less effect on eating behavior than lactate-buffered solutions (14,15).

Chronic inflammation (as indicated by circulating levels of pro-inflammatory cytokines like tumor necrosis factor alpha [TNFα]) also suppresses appetite, and plasma levels of TNFα have been described as being significantly higher in PD patients with lower urea clearance values (Kt/V_{urea}) and those with anorexia (16), although the direction of causality with inflammation is unclear. Patients on PD with *Helicobacter pylori* and anorexia were found to have raised inflammatory markers compared with those without anorexia. Eradication of asymptomatic *H. pylori* in patients with anorexia was also noted as being successful in improving appetite and nutrition (16). Exercise is likely to be an excellent intervention to improve muscle strength and physical function in dialysis patients (17). This is difficult to prescribe, however, and other factors including psychological and functional barriers mean that efforts to

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Received 29 December 2014; accepted 11 April 2015.

encourage physical or resistance activities are frequently overlooked as interventions. Anabolic steroids including megestrol, testosterone, and nandrolone, often at low doses, have shown promise in small studies, resulting in statistically significant weight gain with few apparent side effects, yet there remains little or no consensus on anabolic steroid use or their safety in dialysis patients (18,19). Carnitine is a quaternary amine involved in Co-enzyme A metabolism and therefore in a number of energy pathways involving fatty acids. It is significantly removed by HD (and possibly by PD) and supplementation has been shown to improve nutritional state (20) in a small study.

Dietary assessment is clearly advantageous and advice on snacking and taking small frequent meals is commonly given, yet many PD patients consistently fail to meet nutritional requirements (21). Protein and or calorie supplementation may be helpful, especially during peritonitis. Frequently helpful, but often ignored, is a critical examination of the drug chart, and a strategic reduction in both the quantity and type of medication is sometimes called for (22). Nearly 20% of community dwelling patients over 65 take 10 medications or more, whilst HD patients take a mean of 11 medications (23), and in our experience, PD patients take similar numbers of pills.

DIVERTICULAR DISEASE

The prevalence of diverticulosis increases with age to more than 60% in those aged over 70 (24) and is more common in patients with polycystic kidney disease (25). Interestingly, the distribution of diverticulae within the colon varies, being primarily found in the sigmoid colon in Western patients and predominantly right-sided in Asian populations (26), although the reasons for this are unclear. A high intake of dietary fiber was associated with a lower risk of diverticular disease in 1 study, whist another found the reverse (24). Aspirin, commonly taken by the older patient, has also been found to be associated with an increased risk of developing diverticulitis and diverticular bleeding (24).

A number of otherwise eligible patients are not offered PD due to concerns of enteric peritonitis based on a past history of diverticulitis (27). Wu *et al.* described 72 PD patients in whom there were 4 episodes of fecal peritonitis, 3 of which occurred in patients with >5 diverticulae based on barium enema studies (25). They concluded that diverticulosis was *not* a contraindication to PD. Tranaeus *et al.* described factors that increased the risk of developing enteric peritonitis, including ≥10 diverticulae or the presence of diverticulae ≥10 mm and involving the ascending and transverse colon (28). They postulated that sigmoid diverticulae are more likely to result in gross perforation, whilst non-sigmoid diverticulae more commonly cause micro-perforation. However, here the increased risk could merely be a reflection of the severity of the disease rather than the location of the diverticulae, as this was determined by defining the proximal limit of their distribution. A study of 57 PD patients, 50 of whom underwent barium enema examination, showed no correlation between the presence of diverticulae (found in 48%) and the risk of enteric peritonitis (29). Yip *et al.* found that the presence of diverticulosis (hazard ratio [HR] 5) and diverticulitis (HR 7) involving the ascending colon was an independent risk factor for peritonitis (26). Whilst they suggested that PD might be avoided in this population, those with known high diverticular burden could be covered for gut organisms if presenting with peritonitis. However, this population was specifically being investigated for gut symptoms, and the risks may have been overestimated. Toda *et al.* performed abdominal computed tomography (CT) on 137 chronic kidney disease (CKD) 4/5 patients who were suitable for PD and found ~42% had diverticulae, mainly in the ascending colon. They found that those with diverticulae had an absolute increased risk of peritonitis but this was not due to enteric peritonitis and overall peritonitis rates were low, concluding that the presence of diverticulosis does not affect technique survival in PD (30).

In summary, whilst elderly patients frequently have diverticular disease, unless they are known to have extensive disease (presumably because they have symptoms for which they have been investigated) or have recurrent diverticulitis, they should not be denied the opportunity to try PD, and whilst equivocal evidence exists for fiber supplementation, it may be helpful and is unlikely to be deleterious.

EFFECTS OF PD ON GUT FUNCTION

Gastro-intestinal symptoms appear to be common in all dialysis patients, with reflux being more prevalent in PD patients compared with those on HD (31). Gastric emptying is prolonged in PD patients compared with healthy controls and HD patients, even in the absence of overt symptoms such as nausea or vomiting, and is prolonged when using glucose-based dialysate compared with no dialysate or icodextrin (32). Prokinetic agents (e.g. metoclopramide or erythromycin) may speed gastric emptying and result in a significant increase in albumin and may be helpful in improving intake (33). Intraperitoneal metoclopramide (10 mg up to 4 times/day) has been reported to be useful in resistant gastroparesis secondary to diabetes mellitus in PD patients (34).

Peritoneal dialysis may also exacerbate pre-existing or incipient urinary or fecal incontinence, an increasing problem in older patients affecting both genders. There are reports of cases of fecal incontinence and of rectal and uterine prolapse due to elevated intra-abdominal pressure during PD (35). It is also our observation that ring pessaries used for uterine prolapse can frequently fail at the initiation of PD, requiring a move to a larger size, but this may then interfere with dialysate drainage, although such interference has been rarely reported in the literature. Incontinence often improves with a change from continuous ambulatory PD (CAPD) to automated PD (APD) overnight, and a reduction in daytime dwell volumes may also help, as intra-abdominal pressures are lower when supine (compared with erect). In addition, there are a number of more or less conservative strategies to manage urinary incontinence, but surgical repair often means a temporary or permanent switch away from PD, so it is well worth specifically asking about continence issues prior to catheter insertion (36).

Hernias are well-known complications of PD and their prevalence is higher in PD patients than in the general population. The loss of muscle tone and laxity in connective tissue associated with older patients and the increased intra-abdominal pressures associated with PD increase the incidence of herniation, with rates up to 20%. The rates are lower in APD than in CAPD, however (37).

Long-term effects of PD on the peritoneal surface, with fibrosis and adhesions, may compromise gut function, leading in the worst case to encapsulating peritoneal sclerosis which leads to severe gut complications. Fortunately, this is rare (38).

CONSTIPATION IN THE OLDER PATIENT

Anyone working in PD will be aware of the problems associated with bowel dysfunction that are a common cause of technique failure and poor dialysis efficacy and which predispose to catheter dysfunction and/or malposition. Problems of constipation occur far more commonly in elderly individuals but are often under-recognized and under-reported, yet its consequences and associated costs are substantial (39). There are a number of causes of constipation that are sometimes overlooked and which become more frequent in the older patient including hypothyroidism, hypercalcemia, hypokalemia, stroke, and diabetes with autonomic dysfunction (40). However, prevalence survey data suggest that constipation is up to 3 times *less* frequent in PD patients (29%) compared with those on HD (63%) and around half as frequent as patients with chronic renal failure (CRF) (41,32). Explanations of this somewhat counter-intuitive data are thought to relate to fewer dietary restrictions (resulting in higher fiber), less dehydration (from less stringent fluid restriction), and lower phosphate binder usage (41). In addition, warm dialysate may stimulate bowel motility and increase intra-abdominal pressure, helping with evacuation (42). Constipation in PD patients results in worse health-related quality-of-life measures compared with patients on HD (41). Additionally, constipation and its treatment may facilitate transmural migration of enteric organisms and increase peritonitis, technique failure, and mortality (43). It is also important to note the International Society for Peritoneal Dialysis (ISPD) recommends a drain out and antibiotic prophylaxis to prevent peritonitis for endoscopic examinations due to transmural infection risk (44).

There are numerous drugs that may exacerbate constipation in PD patients including phosphate binders, calcium antagonists, opiates, iron preparations, and anti-depressants. Magnesium salts may be associated with a purgative action, a property that is sometimes helpful.

Diarrhea may contribute up to 13% of all enteric peritonitis episodes (45). Fiber supplements (like psyllium) have been shown to be effective in reducing both laxative requirements and constipation (46) if there is sufficient fluid intake, and these agents can be quite helpful in relief of constipation and are becoming increasingly popular in PD (47). High-fiber foods are rich in phosphates and are sometimes discouraged by dieticians, but these are frequently complexed with phytates, often dramatically reducing their bioavailability, meaning that fiber supplements are gaining popularity since they do not appear to cause the same biochemical issues as phosphates added to processed foods as a preservative (48). Osmotic agents like polyethylene glycol have been shown to be effective in reducing constipation and maintaining bowel frequency and appear safe in PD (48). The use of lactulose was associated with a reduction in peritonitis rates in 1 study, although this does not appear to be by reducing constipation, and differences may be due to changes in intestinal permeability induced by osmotic agents (49). Senna and bisacodyl are commonly prescribed stimulant laxatives that reduce water absorption from the gut. Whilst these agents are likely to be effective at producing bowel movements, they may increase intraluminal pressures. and there is continued debate around the long-term effects of these agents (47). Docusate, a stool softener, is not known to be advantageous in PD patients but is commonly prescribed alongside a stimulant laxative (e.g. senna). However, there is only slim evidence that these agents have any beneficial effects.

CONCLUSION

The older patient on PD faces a number of challenges related to gut dysfunction, which may often be overlooked unless specifically explored, including appetite suppression, constipation, and diverticular disease. Ongoing attention to these aspects of PD patient care may enhance the patient experience, and perhaps even technique and overall survival in this group of patients.

KEY POINTS

- Elderly patients experience reduced appetite and often find reaching caloric goals difficult.
- Gastrointestinal symptoms are common and under-reported in elderly individuals.
- Constipation in older PD patients is associated with an increased risk of peritonitis. Fiber supplements, lactulose and polyethylene glycol appear to be safe and effective as treatments.
- Diverticulosis is common in older patients, but should not preclude PD unless very severe and frequently symptomatic.
- In elderly individuals elevated intra-abdominal pressures associated with PD may exacerbate hernias, urinary incontinence and uterine prolapse which are more common in these groups.

DISCLOSURES

SS has no financial conflicts of interest to declare. SGH has received speaker fees, honoraria and research funding from Baxter.

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