Chapter 6

Dyspepsia — An Underestimated Problem among End-stage Renal Disease Patients

Paulo Roberto Santos

Additional information is available at the end of the chapter

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1. Introduction

Dyspepsia is the most common gastrointestinal disorder in primary medical assistance. In the general population, 40% of people will suffer from dyspepsia during their lifetime [1]. The most frequent category of dyspepsia is functional dyspepsia (FD). Among categories of dyspepsia, FD accounts for roughly 50% of the cases and is defined as dyspeptic symptoms not explained by structural or organic upper gastrointestinal disease [2]. The categories associated with organic alterations of the upper gastrointestinal tract are: reflux disease with normal endoscopy (20%); reflux esophagitis (20%); peptic ulcer disease (10%); and more rarely, Barret's esophagus and malignancy [2].

Dyspeptic symptoms comprise a heterogeneous group of symptoms that have in common their location. The symptoms must be located in the epigastrium and can be included in two syndromes: postprandial distress syndrome (PDS) and epigastric discomfort syndrome (EDS). PDS comprises bothersome postprandial fullness and early satiation; EDS includes epigastric pain or burning. In practice, it is common for symptoms to overlap, and as a rule patients are defined as dyspeptic when suffering symptoms of both syndromes [3]. Heartburn is not considered a dyspeptic symptom, as established in the latest definition by the Rome III consensus in 2006 [4].

The current definition of FD according to the Rome III consensus is the presence of one or more symptoms, with onset at least six months beforehand, being present during the last three months, in the absence of structural disease of the upper gastrointestinal tract (in clinical practice, ruled out by endoscopy and testing for *Helicobacter pylori*). The Rome III consensus gives the definitions of each of the four dyspeptic symptoms (Table 1). Nonetheless, even judicious criteria like these are not totally accurate to diagnose FD. There are reports showing

only modest performance of the Rome III criteria, reaching only 60.7% sensitivity and 68.7% specificity for diagnosis of FD [5].

Symptom	Definition
Postprandial fullness	Unpleasant sensation of prolonged persistence of food in the stomach after a meal
Early satiation	Feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished
Epigastric pain	Subjective, intense and unpleasant sensation in the epigastrium, which can lead patients to believe that some tissue damage is occurring
Epigastric burning	Unpleasant subjective sensation of heat in the epigastrium

Table 1. Definition of dyspeptic symptoms as proposed by the Rome III consensus

Why do I classify FD as underestimated among end-stage renal disease (ESRD) patients? In my view, dyspepsia really deserves special attention among ESRD patients on hemodialysis (HD) for many reasons:

1. The most common non-renal complaints in HD patients are gastrointestinal symptoms, mainly dyspeptic symptoms [6].
2. The negative effect of dyspepsia on quality of life (QOL) is well known [7]. From the perspective of ESRD, the association between dyspepsia and impaired quality of life has greater implications due to central role of QOL among HD patients [8-13].
3. Dyspepsia is also associated with another important condition: nutritional status [14].
4. ESRD allows several lines of investigations about the pathophysiology of FD. The clinical research about the interactions between typical features of ESRD (like neuropathy, uremic toxins, abnormal gut motility and excess of extracellular volume) and FD need to advance [15-23]. Meanwhile, the pathophysiology of FD in ESRD is still not completely understood and the clinical therapy of dyspeptic symptoms typically fails.
5. Treatment challenge of FD is specific in HD patients due to the polypharmacy imposed on these patients, the high prevalence of depressive feelings, which can modulate dyspeptic symptoms, and the multi-factorial mechanisms of uremia acting on the gastrointestinal tract.

Despite the above, from my observations dyspepsia is not routinely screened in dialysis units as is done for cardiovascular disease, osteodystrophy and nutritional status. There is also a lack of randomized, placebo-controlled studies about treatment of FD among HD patients, and a clear explanation of the physiopathological mechanisms regarding FD in ESRD is missing.

In my institution, Federal University of Ceará in Brazil, data have been collected since the 1980s on the relationships between volemic status and gastric motility, especially in animal models, but also among healthy subjects [18-23]. As an attending physician, I have under my care at the dialysis unit of Santa Casa de Sobral Hospital ESRD patients who form an ideal sample for

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studying FD, gastric dismotility and hypervolemia. Thus, currently I am trying to find clinical evidence of the link between the results coming from bench research about the relationships of volemia and gastric emptying with gastroparesis, hypervolemia and FD, which are highly prevalent among HD patients. Therefore, I propose in this chapter to organize bench and clinical data on gastric motility, volume expansion and FD in ESRD patients, to provide insight to help the daily approach to FD among HD patients.

2. How to assess dyspeptic symptoms

Dyspeptic symptoms can be easily assessed by interview. This can be done by applying the Functional Dyspepsia Module [24], one of several diagnostic questionnaires based on the Rome III Consensus [25]. The Functional Dyspepsia Module allows quantitative analysis of dyspeptic symptoms. It contains 18 items. Responses are given according to 4-item and 6-item Likert scales. If a symptom is absent, the respondent skips the questions, so opening the possibility of completing the test without answering all the 18 items. Diagnostic criteria include: one of the symptoms (bothersome postprandial fullness or early satiation or epigastric pain or epigastric burning) with a minimum intensity as assessed by the Likert scale plus a normal endoscopy and a "yes" answer to the "yes-no-questions" about the persistence of a symptom for the past three months, with symptoms' onset at least six months ago.

The Functional Dyspepsia Module is an important and validated diagnostic tool of FD. However, a validated instrument is lacking to specifically detect changes of dyspeptic symptoms over time. This gap could be filled by a kind of patient-reported outcomes questionnaire in line with the Rome III consensus aiming to evaluate the evolution of symptoms. Such a questionnaire would encourage clinicians to routinely check the effects of therapies, and would allow increased studies on treatment of FD. In this sense, it is important to mention a recent pilot study designed to develop a questionnaire to evaluate the outcomes of PDS [26].

3. Impact of dyspepsia on quality of life and nutritional condition

It is well-known that dyspepsia can lower QOL in the general population [7]. In the context of ESRD, quality of life deserves special attention. Compared to the most frequent chronic diseases, like heart failure, angina, diabetes, chronic lung disease, arthritis and cancer, ESRD impairs quality of life the most [27]. Furthermore, high mortality among ESRD patients is stationary despite the recent technical advances in dialysis therapy and the availability of several updated guidelines and recommendations for ESRD treatment. Indeed, in recent years, QOL has become the main outcome of dialysis treatment, either as a self-perceived outcome by the patient or as an objective quality parameter of the dialysis procedure. Unfortunately, many factors associated with low QOL in HD patients are non-modifiable. Consequently, both physical and mental aspects of QOL among HD patients have not been improving during the last decade [12].

My main research line is self-perceived outcomes among HD patients. Since 2006 my research group has been producing studies in this area [8-10, 28-36]. Our sample consists of ESRD patients treated in the only two dialysis units in an area of 34.560 km^2 (37.3 inhabitants/ km^2) in the northern region of Ceará state, northeast Brazil. There we found, as others, a very low level of QOL in HD patients, mainly related to physical aspects. Recently, we presented our results about QOL in dyspeptic patients at the Paulista Congress of Nephrology, in Atibaia, São Paulo, Brazil [37]. We used the SF-36 instrument to evaluate QOL. SF-36 gives results on a scale from 0 (worst result) to 100 (best result) related to eight dimensions of QOL: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health. We used the Functional Dyspepsia Module of Rome III Diagnostic Questionnaires to search for dyspeptic symptoms. Our results showed that physical (bodily pain, general health and vitality) and also mental (role-emotional and mental health) aspects are lower in dyspeptic compared to non-dyspeptic HD patients. Notably, general health and role-emotional are the two dimensions rated below 50 according to the SF-36 scale among dyspeptics. It is exciting to think about FD as a modifiable factor associated with QOL. We urgently need randomized, controlled studies to test the effect of FD treatment on QOL among HD patients.

Another crucial impact of dyspepsia is related to nutritional condition. In the general population, weight loss is taken as an alarm symptom that raises suspicion of organic disease. However, weight loss also occurs in FD [38]. In nephrology, there are many studies on nutrition among HD patients. The most well-known factors associated with malnutrition in ESRD are anorexia and chronic inflammation [39]. FD is not well studied as a factor linked to malnutrition among ESRD patients. We exposed our preliminary data on this question at the Third Conference on Nephrology, held in Valencia, Spain [40]. In our experience, dyspeptic HD patients have a lower calorie and protein intake compared to non-dyspeptics. Like in the case of QOL, it is encouraging to think about FD as a modifiable factor associated with malnutrition, particularly because to same extent FD is easier to treat than anorexia and chronic inflammation. Again, as happens in the context of FD and QOL, clinical trials about the beneficial effects of treating FD on caloric and protein intake are necessary.

4. Hypervolemia and gastroparesis in ESRD: Associated pathways explaining dyspepsia?

As commented above, two groups of dyspeptic symptoms can be distinguished: PDS and EDS. However, in clinical practice there is an overlap between these two groups. Most of the time patients classified as having PDS also present EPS and vice versa [3]. Thus, more than a classification of the symptoms, we need to understand the physiopathological mechanisms involved in order to establish more effective treatment for FD. Gut dismotility can have a central role in the genesis of dyspeptic symptoms among ESRD patients. Moreover, volemic status may be a modulator of gastric emptying.

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The first reports of gastric emptying delay in ESRD appeared at the end of the 1970s [41]. Nonetheless, currently the pathogenesis of gastroparesis in ESRD patients is still unknown. Several features of ESRD have at least a partial role in gastric delay, like anemia, metabolic acidosis and uremic neuropathy [16,17]. However, none of these is considered the main cause of FD, and the treatment of each one of these features is not effective in decreasing the prevalence of FD among HD patients.

In theory, among diabetics on HD features of ESRD act together with alterations of diabetes to cause gastroparesis. Hyperglycemia and decreased action of insulin provoke slow gastric emptying by compromising cellular elements of the stomach (loss or damage of the interstitial cells of Cajal and enteric glial cells), altering motor gastric functions (autonomic neuropathy of the vagal innervations of the stomach), and triggering disturbances of enteral hormones (especially, glucagon-like polypeptide-1) [42]. Despite all this, two facts should be highlighted. First, in primary medical assistance the prevalence of gastroparesis among diabetics is as low as 5% for type 1 diabetes and 1% for type 2 diabetes [43]. Indeed, it is likely that reports of high prevalence of gastroparesis in patients with diabetes are due to a bias caused by reports covering diabetics treated in tertiary medical care. Second, specifically among ESRD patients undergoing HD, the prevalence of FD is the same among diabetics and non-diabetics [15,44,45]. In the future perhaps a specific therapy for gastroparesis among diabetics could be developed, targeting alterations of gastric motility provoked by diabetes. However, as things now stand except for glycemic control, treatment of FD and gastroparesis does not differ between diabetics and non-diabetics on HD.

One attractive hypothesis is that volemia is the main modulator of gastric motility, and that hypervolemia elicits gastroparesis. Since ESRD is typically a condition of excessive extracellular volume, this hypothesis could explain the high prevalence of FD among patients on HD (the prevalence is nearly 70%) [15]. It also opens a field for therapeutic strategies to control extracellular volume among HD patients, aiming to relieve dyspeptic symptoms. At the Federal University of Ceará, researchers from the Department of Physiology and Pharmacology of the Faculty of Medicine have been performing experiments to understand the relationships between extracellular volume and gastrointestinal motility during the past 35 years. Data have been accumulated suggesting a negative correlation between extracellular volume and gastric emptying time, especially in animal models (see Table 2 for details about the method of evaluating gastric emptying in rats), but also in humans. Results converge to clearly show that hypervolemia decreases gastric and intestinal motility [18-23]. Neural and humoral pathways have been suggested to explain this correlation [21]. Also, gastric motility and permeability are closely related, and hypervolemia increases secretion of fluids and electrolytes while dehydration decreases secretion [46-48]. Healthy blood donors make good subjects for *in vivo* experiments to test the relationship between volemic status and gastric emptying [23]. Among them, it was found that gastric compliance (measured by barostat) increases after donating 450 ml of blood (functioning as acute hypovolemia). Conversely, compliance returns to physiologic levels after infusion of the same volume of saline.

No doubt ESRD patients compose an ideal model to study the effects of hypervolemia on gastric motility *in vivo*. The drawback is the lack of simple and accurate methods for

assessing volemia in clinical studies. Table 3 shows the available clinical tools for detecting hypervolemia.

• 1.5 ml of the test meal (0.5 mg mL^{-1} phenol red in 5% glucose solution) given orally through a stainless steel tube
• Animals killed by i.v. thiopental overdose at 0 (standard) or 10 min after the test meal
• Stomach exposed by laparotomy, clamped at the pylorus and cardia ends, and excised
• Removed stomach placed in 100 ml of 0.1 $_N$ NaOH, cut into small pieces and homogenized for 30 seconds
• Settling for 30 min
• 10 ml of the resulting supernatant centrifuged for 10 min (2800 r.p.m.)
• Proteins in 5 ml of this supernatant precipitated with 0.5 ml of trichloroaetic acid, centrifuged for 20 min and 3 mL of the supernatant added to 4 mL of 0.5 $_N$ NaOH
• Absorbance of the sample read at a wavelength of 560 nm by spectrophotometry
The formula for calculating gastric emptying:
• % Gastric emptying = 1 – [(amount of phenol red covered from test stomach)/ (average amount of phenol red covered from standard stomachs] x 100
Standard stomachs:
• Rats killed immediately after gavage

Table 2. Step-by-step description of the method for measuring gastric emptying of liquid in rats

Atrial natriuretic peptic
Cyclic guanidine monophosphate (post dialysis level higher than 20 pmol/L indicates fluid overload)
Bioimpendane analysis
Blood volume monitoring (change in hematocrit or protein during hemodialysis procedure)
Inferior vena cava diameter (by echocardiography)

Table 3. Tools for clinical estimation of fluid overload

Based on results of bioimpedance analysis, we have shown that among HD patients, relative fluid overload higher than 15% is associated with higher prevalence of FD compared to patients with lower fluid overload (66% *versus* 34%) [49]. Figure 1 shows the bioimpedance device used by us: a body composition monitor specifically designed to assess extracellular water in patients with kidney failure. In addition, we found that dyspeptic patients on HD present longer gastric emptying time compared to non-dyspeptics (238 minutes *versus* 185 minutes) [15]. Since gastric dismotility seems to be crucial to trigger FD, and due to the complexity of measuring gastric emptying time *in vivo*, I summarize this study below.

The simplicity of assessing FD by interview contrasts with the complexity of assessing gastric emptying time *in vivo*. The tools available for clinical estimation of gastric emptying time are: technetium-99m scintigraphy (gold standard) [50]; time of appearance of acetaminophen in blood after its ingestion [51]; imaging studies using 3D ultrasonography and nuclear resonance [52, 53]; the smart pill (which seems to be a practical and promising method) [54]; and octanoic

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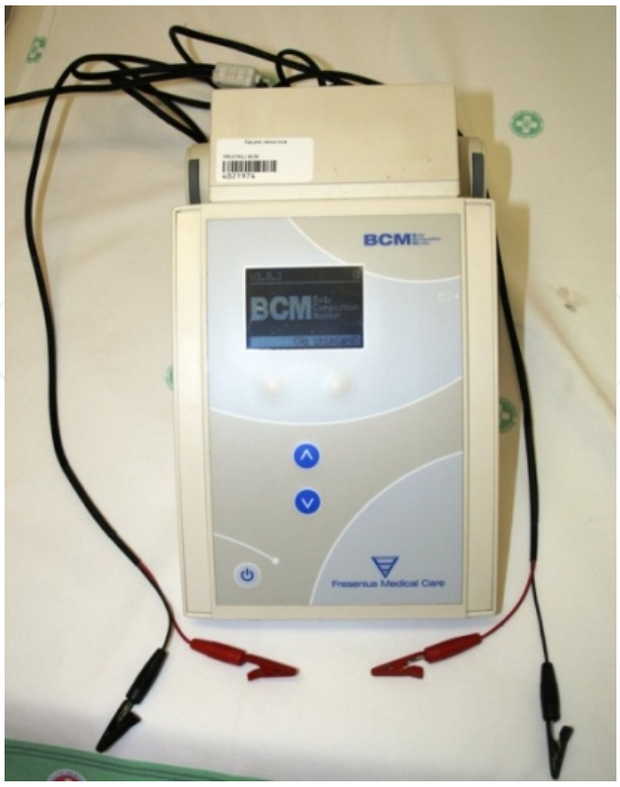

Figure 1. Body Composition Monitor® by Fresenius

acid breath test using ^{13}carbon (a very attractive method with 89% sensitivity compared to the gold standard technetium-99m scintigraphy) [55]. We used the last method in our study to assess gastric emptying time in a sample of HD patients from our clinic [15]. See Table 4 for details about the method of evaluating gastric emptying time in humans. Patients ate a scrambled egg with carbon linked to octanoic acid. Octanoic acid remains firmly attached to the egg in its passage through the stomach, but after that it is absorbed in the duodenum and eliminated in the breath. Patients breathe into bags before the test meal (baseline), every 15 minutes during 2 hours and then every 30 minutes for a further 2 hours. The gastric emptying time was defined by half-emptying time (the so-called T ½). T ½ is the time in minutes for the first half of the carbon dose in the test meal to be eliminated. Dyspeptic symptoms were assessed by a validated Brazilian version of a standardized questionnaire named the Porto Alegre Dyspeptic Symptoms Questionnaire (PADYQ). We found longer T ½ (longer gastric emptying time) among dyspeptics compared to non-dyspeptics. Moreover, we found a positive linear correlation between T ½ and dyspepsia score, in other words, the longer the gastric emptying time, the more severe the dyspeptic symptoms [15].

In short, the series of studies at our university demonstrate two findings to support clinical approaches to FD among ESRD patients: first, hypervolemia elicits gastric emptying delay [18-23]; second, dyspeptic patients on HD have longer gastric emptying time and higher fluid overload than non-dyspeptics [15, 49]. Table 5 summarizes the body of evidence on the relationships between volemia, gastric motility and dyspepsia produced in my Institution.

• Patients are instructed to avoid smoking and eating foods rich in C-4 plants, like corn (including baked goods made with cornmeal) and pineapples, in the week before the study
• For the test: a minimum of 10 hours of fasting
• The test meal consists of a scrambled egg with the yolk labeled with 100 μg of ^{13}carbon octanoic acid (after homogenizing the yolk, the egg white is added, beaten and baked)
• The test meal is ingested with 60 g of white bread and 5 g of margarine during 1 to 5 min and followed immediately by 150 mL of water
• To collect the breath samples, the patient exhales into closed aluminized plastic bags, before the test meal (baseline), and then at 15-minute intervals during 2 hours and then every 30 min for a further 2 hours
• Patients are advised to remain seated and refrain from physical activity during the test
• The gastric emptying time is defined by half-emptying time (T ½)
The formula for calculating T ½:
• T ½ = time in minutes for the first half of the ^{13}carbon dose in the test meal to be metabolized
The cut-off:
• T ½ of more than 200 minutes identifies gastric emptying delay

Table 4. Step-by-step description of the method for measuring gastric emptying time in humans

Evidence	Sample	Year [Reference]
Gastric compliance is modulated by blood volume	Anesthetized dogs	1983 [18]
Blood volume expansion decreases gastrointestinal flow while blood volume retraction increases it	Rats	1990 [19]
Expansion of blood volume delays gastrointestinal transit	Awake rats	1998 [20]
Vagal pathway is involved in the delay of gastric emptying elicited by acute blood volume expansion	Awake rats	1999 [21]
Stomach is an adjustable reservoir according to blood volume level	Anesthetized rats	2002 [22]
Acute blood shedding increases gastric compliance	Humans (healthy subjects)	2005 [23]
Gastric emptying delay is associated to functional dyspepsia	Patients on hemodialysis	2013 [15]
Fluid overload is associated to higher prevalence of functional dyspepsia	Patients on hemodialysis	2013 [49]

Table 5. Studies of volemia, gastric motility and dyspepsia produced at Federal University of Ceará, Brazil

5. Treatment

Confirming our finding that dyspepsia is underestimated despite the well-known impacts of FD on QOL and nutritional condition, there is a lack of randomized, placebo-controlled studies of treatment strategies for FD in ESRD patients. Most data on treatment of FD come from studies in the general population. This fact is worrying due to many peculiarities of uremia and its effects on gastrointestinal tract. Nevertheless, a common finding in the general population and among dialysis patients is the inefficiency of drug therapy. Only half of the

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dyspeptic patients become asymptomatic in population samples [56]. This is similar to our finding of 60% symptomatic HD patients under treatment for FD [15].

Initial treatment of FD in HD patients is usually empirical after performing an endoscopy to exclude ulcer (and other sorts of organic lesions) and a test for absence of *Helicobacter pylori*. The first step for treating FD can be to try acid-suppression therapy, either by an H2-receptor antagonist (H2-RA) or proton pump inhibitor (PPI) [57,58]. Favoring the initial use of PPI instead of H2-RA is the consensus of the superior acid secretion suppression of PPIs over H2-RAs. Favoring acid suppression therapy is the recent evidence coming from studies in healthy subjects that acid secretion can impair gastric motility [59,60]. Thus, theoretically PPIs can ameliorate FD by acting on both pain and dysmotility-like symptoms. Even though widely used clinically, the double-dose of PPIs in case of persistence of dyspeptic symptoms is not supported. There are reports that standard and double doses have the same results [61].

Effective	Ineffective	Under investigation
Metoclopramide (not tolerated in some) [64,71]	Mosapiride [65]	Acotiamide [69]
Domperidone (not used in USA) [57]	Tegaserod [66]	
Levosulpiride [63]	Itopride [67]	
	ABT-229 [68]	

References in square brackets

Table 6. Prokinetics for relief of dyspeptic symptoms

Prokinetics can be a second drug to add to PPI in case of treatment failure, or the first option if PDS is the main clinical presentation, or in most cases of overlap of PDS and EDS. At least, two drugs are individually superior over placebo in the treatment of FD: domperidone and cisapride [57]. Unfortunately, the accumulated data on the effects of cisapride (one of the most studied prokinetics) is of no value since the use of cisapride has been withdrawn due to risk of arrhythmia [62]. Domperidone is used in Brazil, but it is not available in many countries including the United States. A newer drug named levosulpiride shows the same positive results found with the use of cisapride [63]. In our daily practice, we prefer an old drug in use since 1960, metoclopramide. Metoclopramide is traditionally used for gastroparesis in diabetics before each meal and at bedtime, and has proven to improve the nutritional status in non-diabetics on dialysis [64]. However, metoclopramide has a limitation on its use, because it can provoke dyskinesia. New prokinetics, like mosapride, tegaserod, itopride and ABT-229, seem to be no better than the former drugs [65-68]. Currently, acotiamed is under investigation [69]. In comparison to PPIs, prokinetics have no advantage in the treatment of dyspepsia, based on studies performed in the general population [70]. However, in light of the extensive evidence of the close relationship between gastric delay and FD in ESRD discussed previously, it is my opinion that prokinetics should have a leading role in the treatment of FD in patients undergoing HD. Furthermore, there are reports favoring prokinetics regarding improvement of nutritional condition in ESRD patients [64,71]. Table 6 shows a list of effective, ineffective and under-investigation prokinetics.

Among the peculiarities of FD in ESRD patients, there is the extensive list of stressors associated with HD: illness effects, dietary constraints, time restriction, functional limitations, changes in employment, sexual dysfunction, and high mortality [13]. This explains why depression and anxiety are highly prevalent among HD patients [9,11]. Anxiety and depression can be manifested by dyspepsia (somatization). This fact forces the inclusion of depression in the differential diagnosis of FD alongside gallbladder, pancreatitis, medications, and hepatobiliary causes. On the other hand, dyspeptic symptoms of FD are more likely to be severe in depressive patients. There are several studies showing benefits of anxiolytics and antidepressants, especially tricyclic antidepressants, in the relief of dyspeptic symptoms, although their results are not superior to those of PPIs or prokinetics in the general population [72]. Once again, we have to be careful to extrapolate these population data to specific samples of ESRD patients. Due to the previously reported list of associated stressors and high prevalence of depression among HD patients, it is plausible that the effects of antidepressants can be more pronounced among HD patients than in the general population. Taking two specific drugs: amitriptyline (tricyclic antidepressant) and sertroline (selective serotonin reuptake inhibitor antidepressant) can be effective. Amitriptyline ameliorates dyspeptic symptoms in subjects who did not obtain relief with antacids and prokinetics [73]. Sertroline is a very attractive drug to test for FD in HD patients because of its additional effect of decreasing the serum level of interleukin-6 in HD patients on HD [74]. However, treatment of depression among HD patients is not simple. Drug therapy alone for depression has proven to be ineffective among HD patients. One of the reasons is that drug therapy by itself cannot eliminate the powerful stressors associated with HD therapy. For instance, among women undergoing HD, the sole use of drugs for depression will fail if there is not a concurrent approach to sexual dysfunction [75]. To my thinking, it is clear that treatment of FD in HD patients should include screening for depressive symptoms, and if depression exists, psychotherapy is necessary along with the use of drugs. Supporting this opinion, psychotherapy was proved to be beneficial for FD in controlled random trials [76].

6. Alternative medications and emerging therapies

Due to high therapy failure and risk of drug side effects from FD treatment, alternative medicine is attractive. Alternative medicine includes herbal medicine, traditional Chinese medicine and the emerging therapies, especially invasive procedures for gastroparesis.

STW 5 (also known as Iberogast) is one of the most studied mixtures of herbs proven to be effective in relieving dyspeptic symptoms. The main and active ingredient of STW 5 is *Iberis amara*, which acts both to reduce acid secretion and accelerate gastric emptying [77]. The last action is a result of its different effects on gastric portions, inhibiting the proximal portion of the stomach while exciting the tonus of the distal stomach [78]. Its prokinetic action is similar to cisapride [79]. Usual dosage of STW 5 is 20 drops three times a day. Data on other alternative medications are limited, such as artichoke leaf extract, blend of peppermint oil and caraway oil, banana powder capsules, and antioxidant astaxanthin [80].

Less available in other cultures, Xiaoban Xiatang and Zhizhu Tang are the two herbal infusions most used by traditional Chinese physicians to treat dyspeptic symptoms [81]. However, regarding traditional Chinese medicine, acupuncture is undoubtedly the procedure that deserves most attention. It has been shown that acupuncture accelerates gastric emptying time and reduces postprandial fullness, early satiety and bloating [82].

Among emerging therapies for gastroparesis, there are invasive procedures like gastric electrical stimulation and pyloric botulinum toxin injection. Gastric electrical stimulation consists of surgical implantation of electrodes into the muscle layer of the gastric antrum. A pulse generator in the abdominal wall delivers low-energy electrical pulses at high frequency to the electrodes. Meta-analyses have shown benefits of this technique, and isolated studies have demonstrated improvement of dyspeptic symptoms, quality of life, weight, body mass index and albumin level [83-86]. Gastric electrical stimulation seems to work less because of its motor effects on gastric motility, and more because of its effects in altering the sensory function of afferent nerves of the stomach. Surgical complications occur in 10% of cases, indicating that this method should be prescribed only for refractory cases and not as routine therapy. Another invasive procedure for gastroparesis is the injection of the botulinum toxin (botox) in a circumferential manner into the pyloris. Due to its effect of inhibiting acetylcholine release, botox accelerates gastric emptying and improves dyspeptic symptoms in open-label trials [87-89]. The procedure consists of intrapyloric injection of 100-200 units of botox during endoscopy and has been proven to be safe. However, botox injection cannot be currently recommended since at least two double-blind placebo controlled studies showed the same effects of botox and placebo [90,91]. Table 7 summarizes the treatment options for FD.

Established interventions
Antacids
Prokinetics
Antidepressants
Psychotherapy
Alternative medicine
Acupuncture
STW 5 (Iberogast)
Xiaoban Xiatang
Zhizhu Tang
Artichoke leaf extract
Peppermint oil + caraway oil
Banana powder capsules
Antioxidant astaxanthin
Emerging therapies for gastroparesis
Gastric electrical stimulation
Pyloric botulinum toxin injection

Table 7. Treatment options for functional dyspepsia

7. How to treat: My opinion

It is clear that the traditional algorithm indicating use of anti-secretory agents for ulcer-like FD and prokinetics for dysmotility-like FD does not meet the complexity of FD in the context of ESRD. The ordinary exclusion of patients with inadequate dialysis clearance from studies about FD implies that hypervolemia can be involved in the high prevalence of FD in the cases of more typical patients on HD (those excluded from the studies). In these cases, hypervolemia could trigger gastric emptying delay. I think that patients on HD with FD should first have their dry-weight re-evaluated. Indeed, FD can be an extra tool to help estimate real dry-weight of our HD patients. Second, metoclopramide can be used before each meal and at bedtime. Its beneficial effects on nutritional status are widely documented [62,69]. Third, screening for depressive symptoms and psychotherapy are essential in the treatment of FD among HD patients. Concerning anti-depressant drugs, sertraline is a good option because of its anti-inflammatory effects. Finally, acupuncture can be tried to ameliorate dyspeptic symptoms. Acupuncture's action in accelerating gastric emptying is particularly attractive.

8. Conclusion

Dyspepsia is highly prevalent among ESRD patients undergoing HD. It can affect central aspects, like QOL and nutritional status. The division of FD into PDS and EDS is didactic but not reasonable in clinical practice. The fact is that most dyspeptic patients present symptoms of both syndromes. Treatment is known to be ineffective. Therapy directed toward the main physiopathological pathways can be crucial, yet the pathogenesis of FD in ESRD remains virtually unknown. Gastroparesis seems to be important, independent of the presence or absence of diabetes. The association of actions to accelerate gastric emptying and to improve depressive feelings should be more effective than traditional treatment algorithms. The hypothesis is that the relief of dyspeptic symptoms would lead to better QOL and nutritional status.

Author details

Paulo Roberto Santos[1,2*]

Address all correspondence to: prsantos@fortalnet.com.br

1 Sobral Faculty of Medicine, Federal University of Ceará, Sobral, Brazil

2 Dialysis Unit, Santa Casa de Sobral Hospital, Sobral, Brazil

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