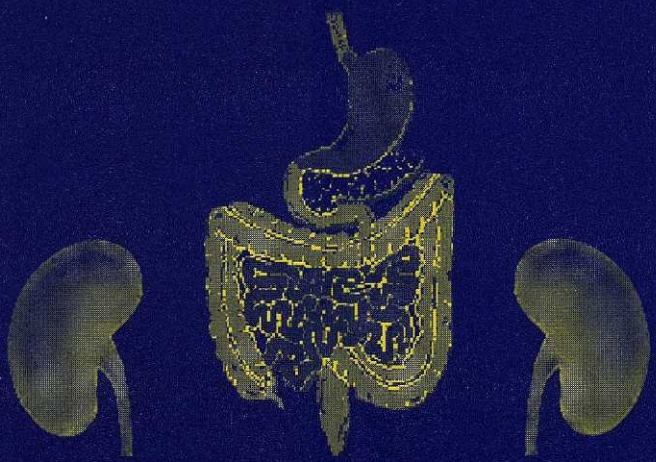
GASTROINTESTINAL SYMPTOMS IN CHRONIC RENAL FAILURE

Prevalence and pathophysiological mechanisms



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Göteborg 2003

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ABSTRACT

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Chronic renal failure (CRF) has a varying etiology and is characterised by an increasing accumulation of toxic metabolic waste products in the blood. Malnutrition is a common finding in uraemic patients and is regarded as a marker for morbidity and mortality. Many factors, including gastrointestinal (GI) symptoms, lead to malnutrition in CRF.

The aims of the present study were to evaluate the prevalence of GI symptoms in CRF patients and to find possible pathophysiological mechanisms behind these symptoms.

Gastrointestinal symptoms and psychological well-being were assessed with the aid of two questionnaires. The use of acid-suppressive therapy was evaluated by interviewing the patients and by reviewing medical records. Motility of the small intestine was measured by means of antroduodenojejunal manometry. Radiopaque markers were used to assess gastric emptying. Aspirate from the jejunum for culture was obtained through the manometry catheter.

Gastrointestinal symptoms were more common in CRF compared with reference values from the general population. A relationship between GI symptoms in CRF patients and reduced psychological well-being was observed.

There was an overuse of acid-suppressive drugs in dialysis patients and the majority of the indications were inappropriate, with non-specific GI symptoms as a dominating indication. Long-term treatment, more than eight weeks, was predominant.

Manometry of the small intestine revealed neuropathic-like motor patterns in 50% of patients. A high proportion of long clusters was observed during phase II as well as a high proportion of retrograde pressure waves in phase II and post-prandially in CRF, both in symptomatic and asymptomatic patients. Accelerated propagation velocity of the activity front of MMC in the duodenum correlated with GI symptoms. Small intestinal bacterial overgrowth (SIBO) was found in 36% of CRF patients irrespective of GI symptoms. A neuropathic-like motor pattern was more commonly observed in CRF patients with SIBO.

A delay in gastric emptying was disclosed in patients with CRF, especially in men. Gastric emptying was not correlated to GI symptoms. A delay in emptying was more common in patients on peritoneal dialysis. Helicobacter pylori did not affect gastric emptying.

Conclusions: Gastrointestinal symptoms are common in CRF patients and are associated with impaired psychological well-being. Overuse of acid-suppressive therapy is common in CRF patients. Abnormal small bowel motility, delayed gastric emptying and SIBO are common findings in CRF patients. Some abnormal motility findings were related to GI symptoms and may be involved in the pathophysiology of GI symptoms in CRF.

Key words: Chronic renal failure; end-stage renal disease; gastrointestinal symptoms; overuse; proton pump inhibitors; H2-receptor antagonists; quality of life; manometry; small intestinal bacterial overgrowth; gastric emptying; Helicobacter pylori.

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Prevalence and pathophysiological mechanisms

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I. **The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well-being**
Strid H, Simrén M, Johansson A-C, Svedlund J, Samuelsson O, Björnsson ES.
Nephrol Dial Transplant 2002;17: 1434-1439

II. **Overuse of acid suppressant drugs in patients with chronic renal failure**
Strid H, Simrén M, Björnsson ES.
Nephrol Dial Transplant 2003; 18: 570-575

III. **Patients with chronic renal failure have abnormal small intestinal motility and a high prevalence of small intestinal bacterial overgrowth**
Strid H, Simrén M, Stotzer P-O, Ringström G, Abrahamsson H, Björnsson ES
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Gastrointestinal symptoms in chronic renal failure – Prevalence and pathophysiological mechanisms.

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"Even things that are true can be proved"
(Oscar Wilde)

Gastrointestinal symptoms in chronic renal failure, prevalence and pathophysiological mechanisms

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LIST OF PAPERS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

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CONTENTS

ABBREVIATIONS

AST	Acid-suppressive therapy
BMI	Body Mass Index
CCK	Cholecystokinin
CI	Confidence interval
CRF	Chronic renal failure
OGD	Oesophagogastroduodenoscopy
EGG	Electrogastrography
ESRD	End-stage renal disease
GORD	Gastro-oesophageal reflux disease
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSRS	Gastrointestinal Symptom Rating Scale
HD	Haemodialysis
Hp	Helicobacter pylori
H_2-RAs	H_2-receptor antagonists
HRQOL	Health-related quality of life
IBS	Irritable bowel syndrome
IQR	Interquartile range
MMC	Migrating motor complex
NS	Not significant
NSAIDs	Non-steroidal anti-inflammatory drugs
QOL	Quality of life
PD	Peritoneal dialysis
PGWB	Psychological General Well-Being
PPIs	Proton pump inhibitors
ROMs	Radiopaque markers
SEM	Standard error of the mean
SIBO	Small intestinal bacterial overgrowth
vs	Versus

"Chronic renal failure" is used alternatively with "end-stage renal disease", "uraemic" and "renal insufficiency" and does not indicate a difference in renal function.

INTRODUCTION

Chronic renal failure (CRF) is caused by a number of pathophysiologic mechanisms and disease processes. Many clinical, biochemical and metabolic consequences of CRF are predictable, but not specific to the underlying renal disease. As the loss of nephrons proceeds in renal failure, the glomerular filtration rate decreases and several metabolic waste products are retained. Patients with these retained products are at increased risk of developing a variety of metabolic abnormalities with high rates of morbidity. Fluid retention and tubular dysfunction ultimately lead to life-threatening pH and electrolyte imbalances. Substitution of the native kidney function must be provided and dialysis is the mainstay of therapy. The intention of dialysis therapy is to remove the waste products and water. Peritoneal dialysis (PD) and haemodialysis (HD) are the two types of dialysis currently used. During these two dialysis methods the metabolic waste products are cleared over a membrane, in HD over an artificial membrane outside the body and in PD over a biological membrane, the peritoneal membrane of the patient. In PD a hyperosmotic solution, containing electrolytes, lactate, and an osmotic agent (usually glucose), is infused into the abdominal cavity several times daily through a permanently-implanted, intraperitoneal catheter. A rather high proportion of the intraperitoneal glucose is absorbed, resulting in increased blood glucose levels and an important additional energy intake. At the end of 2002, 3,215 people in Sweden were on dialysis, 2,434 (76%) HD and 781 (24%) PD (3). The annual increase of dialysis-dependent chronic renal failure is about 5% in Sweden (3). Two-thirds of the patients were men and one-third women, with a mean age of 56 years and without any difference between men and women.

Chronic renal failure has an important impact on the GI tract. Patients with CRF often have a variety of GI problems. Gastrointestinal symptoms, such as nausea, vomiting, dyspepsia, diarrhoea and abdominal pain, have been reported in individuals with CRF (1, 5, 87, 156). However, the available data on the prevalence of GI symptoms are limited and incomplete. Although these symptoms are very common, the pathophysiological mechanisms of GI symptoms in CRF are far from understood. An increased prevalence of peptic ulcer and disturbed GI motility have been demonstrated but the results are conflicting.

Limited knowledge exists of the prevalence and pathophysiology of GI symptoms in CRF. A larger population of CRF patients and various techniques for studying upper GI motility offer a possibility to better understand the clinical and pathophysiological aspects of GI symptoms in CRF.

1. THE GI TRACT IN CHRONIC RENAL FAILURE

1.1. Prevalence of gastrointestinal symptoms

Patients with end-stage renal disease (ESRD) often have GI complaints. Evaluation of GI symptoms in CRF patients has demonstrated a high prevalence, with values from 32% to almost 80% (1, 5, 87, 130, 156, 226). Dyspeptic symptoms, such as nausea, vomiting, abdominal distension and early satiety, are the most frequent complaints and these have been examined most widely. However, the majority of these studies have been performed in haemodialysis patients (1, 87, 130, 156, 226) and the presence of GI symptoms in PD patients and predialytic patients is not well studied. Furthermore, these studies do not include comparisons of GI complaints in HD patients, PD patients, predialytic patients and control groups.

1.2. Structural changes of the upper GI tract

The effects of CRF on the GI tract can be divided into dialysis-related and complications that are more systematically related. The majority of complications are likely to be related to the latter and will be discussed below.

Endoscopic signs of gastroduodenal lesions, such as erythaema, petechiae and erosions, are common in patients on dialysis (145, 149, 198). Histological gastroduodenitis occurred in nearly half of all uraemic patients regardless of dialysis treatment or not (145, 232).

The prevalence rates of gastrooesophageal reflux disease, both endoscopic and histologic oesophagitis, are similar in uraemic and non-uraemic patients (35, 198).

An association between peptic ulcer disease and CRF was suggested in the early days of dialysis (77, 185). However, these reports were based on radiological studies on small numbers of patients. More recent studies using endoscopy have concluded equal incidence of peptic ulcers in CRF patients and in the general population (4, 7, 145). The prevalence of peptic ulcer in predialytic patients is unexplored.

The incidence data of gastrointestinal bleeding in uraemic patients on dialysis are insufficient. Haemorrhagic gastroduodenopathy and angiodysplasia

are common sources of upper GI bleeding in CRF patients (36, 238, 239). The mortality rate in upper GI haemorrhage is significantly higher in CRF patients than in the general population, probably due to more fragile patients with an impaired haemostasis (26, 220).

1.3. Gastrointestinal peptides

A number of polypeptide hormones are involved in the regulation of motility, secretion and blood flow within the GI tract (53). Alterations in the gastrointestinal hormone profile in CRF patients, including elevated gastrin, cholecystokinin, secretin, motilin, neurotensin and pancreatic polypeptide levels have been well documented (75, 92, 161, 163). The importance of these alterations in motility and secretory disturbances of the GI tract in CRF is unclear.

After a meal, however, gastrin increases and stimulates acid secretion and GI motor activity by increasing antral contractions and disrupting fasting motility (150). The acid hypersecretion and the post-prandial motility pattern result in delayed gastric emptying (146). At very high doses, similar to those observed in CRF, gastrin stimulates contractions of the upper GI tract as well as gastric acid and pancreatic exocrine secretion (171).

Motilin is considered to be involved in the cyclic pattern of the MMC in the upper GI tract (166), and also stimulates colonic motor activity (225). Cholecystokinin, which is increased in CRF, acts as a regulator of solid and liquid gastric emptying in humans (25).

2. MALNUTRITION

Protein-energy malnutrition is common among patients on both haemodialysis and peritoneal dialysis, with prevalence rates varying between 20 and 55% in different reports (5, 15, 39, 134, 216, 235). Severe malnutrition is present in approximately 5 to 10%, and moderate malnutrition in an additional 20 to 45% of patients. Malnutrition is a strong predictor of morbidity and mortality in patients on maintenance dialysis (2, 129).

Low serum albumin levels are one of the strongest predictors of morbidity and mortality, both in HD patients (9, 129) and PD patients (9, 200), and has been considered as an important marker for malnutrition. However, low plasma albumin concentration in CRF patients does not necessarily reflect only the nutritional status. In fact, albumin is a negative acute-phase reactant, and this

implies that any intercurrent acute disease (indicated by a rise in C-reactive protein) will lower serum albumin levels (107). Furthermore, serum concentrations of several acute phase proteins are increased in CRF patients (52). Concomitant liver disease in patients with CRF can also affect serum albumin levels.

There is no single definite marker for malnutrition in uraemic patients and nutritional assessment relies on clinical, dietary, anthropometric, biochemical factors and estimates of body composition.

3. GASTROINTESTINAL MOTILITY

3.1. Basic concepts

The major function of the digestive system is to receive and digest food, absorb dietary nutrients and expel indigestible remains. The motility of the GI tract is a prerequisite for digestion and absorption. In general, two basic types of movements occur in the gastrointestinal tract – mixing movements, which keep the intestinal contents thoroughly mixed and propulsive movements, which cause the food to move forward. The mixing movements are caused by either peristaltic contractions or localised contractions of small segments of the gut wall. The basic propulsive movement of the gastrointestinal tract is peristalsis, which can be looked upon as a moving contractile ring that appears around the gut (135). Two types of contractions can be distinguished, phasic with a short duration and tonic with more sustained duration (110).

The intestinal smooth muscle cells exhibit regular depolarisations and repolarisations of the membrane potential, called the intestinal slow wave, which constitute the electrical basis for contractions in the gastrointestinal tract. The slow waves determine the frequency and direction of contractions, but are not able to cause smooth muscle contraction directly. To provoke a contraction, spike potential superimposed on the slow wave depolarisation is needed (88). The intestinal slow waves act as pacesetters and the frequency varies in different parts of the gut, from approximately 3/min in the human stomach to 12/min in the duodenum (233). The motor pattern of the upper gastrointestinal tract differs during fasting and after feeding. In the fasting state there is a cyclic motor activity called the migrating motor complex (MMC) (210). The three phases of the MMC are defined according to the following criteria; **phase I**, a period of motor quiescence ($\leq$ 2 contractions/10 min) following a phase III period, **phase II** with intermittent and irregular contractions preceding phase III and **phase III** or the activity front, with propagated motor activity at maximal frequency with a

duration of at least two minutes at the level of the Treitz ligament. The interdigestive motor pattern was early on given the role of an "intestinal housekeeper".

Eating interrupts the interdigestive cycle, which is replaced by an apparently random occurrence of motor events, called the post-prandial or fed motility. The post-prandial motor pattern is similar to the interdigestive phase II (109). The function of post-prandial small intestinal motility is to transport the chyme to the colon and to optimise the conditions for digestion and absorption in the small intestine.

3.2. Study methods of gastrointestinal motility

In recent decades important advances have been made in understanding both the normal physiology of the alimentary tract and the pathophysiology of different gastrointestinal disorders. In particular, techniques to evaluate gastrointestinal motility have been developed. The most important methods will be described below.

There are many tests to assess gastric motor function. In order to study gastric emptying, several methods have been used. Scintigraphy is perhaps the most physiological method for measuring gastric emptying of liquid and solids (40, 91). However, this method is expensive and of limited availability. An alternative method for measuring gastric emptying is to use indigestible radiopaque markers (64). This method has demonstrated a close correlation with scintigraphic emptying of solids (204). Breath tests have recently been developed to measure gastric emptying (71). The gastric myoelectrical activity generated by smooth muscles (as reflected by the gastric slow waves) can be measured with mucosal, serosal or cutaneous electrodes, electrogastrography (EGG) (66, 126, 167).

Manometry techniques to study lumen-occlusive contractions in different parts of the gastrointestinal tract, both in clinical settings and in research, are widely used. In the small bowel and in the colon both stationary techniques, with external transducers (215) and water-perfused tubes (11, 31), and ambulatory techniques (127, 169) are available. As an indirect measure of gastrointestinal motility, different transit studies, including radiopaque markers, scintigraphy and breath tests are used to assess the time taken for food or other material to pass a specified part of the gastrointestinal tract (8, 132, 179).

3.3. Oesophagus and stomach

Most studies of motility in chronic renal failure have focused on the gastric motor function and there are only a few reports on disturbed motility in the oesophagus. One study from Greece showed disturbed contractions in the lower part of oesophagus in asymptomatic HD patients compared to controls (188).

Several studies have been performed on gastric emptying in CRF patients. These studies have demonstrated somewhat conflicting results. However, delayed gastric emptying was found in the majority of these studies (16, 27, 45, 54, 106, 183, 226, 228) and only a few have reported normal gastric emptying (197, 214, 236). Scintigraphy was the method most commonly used (16, 45, 106, 197, 214, 236), but breath tests, radiopaque markers and ultrasound have also been used in studies on gastric emptying in patients with CRF (27, 54, 183, 226, 228). Most of these studies have failed to demonstrate an association between GI symptoms and delayed gastric emptying. However, van Vlem and co-workers found a correlation between dyspepsia and delayed gastric emptying in HD patients (226). Furthermore, improved serum albumin levels (174, 189) and fewer GI symptoms (44) were achieved after treatment of gastroparesis in non-diabetic dialysis patients. Moreover, a relationship between delayed gastric emptying and biochemical markers of nutrition has previously been demonstrated (45).

The emptying function of the stomach is controlled by gastric myoelectrical activity, and abnormal activity, as measured by EGG, has been reported in both children (170), and adults (126, 167) with CRF. However, in a recent study demonstrating delayed gastric emptying in PD patients no association with abnormalities in post-prandial EGG was found (66).

3.4. Small bowel

The patterns of normal small bowel motility in humans are rather well described (100), but marked inter- and intra-individual variations make interpretation difficult and limit the use in clinical practice (109, 116). Antroduodenojejunal manometry is used when conventional diagnostic tools have failed to demonstrate an organic disease (32, 143).

Manometry has an important role in clinical investigation of patients with suspected intestinal pseudo-obstruction (201). Gastrointestinal manometry has also been used in patients with diabetes mellitus, gastroparesis, liver cirrhosis, and idiopathic gastroparesis (33, 114, 131).

Furthermore, manometry has been conducted in functional bowel disorders in order to find specific pathophysiological motility patterns. In patients with IBS, the periodicity of MMC during the daytime has been found to be shorter in diarrehoea-predominent patients (112, 113) and longer in IBS patients with predominant constipation (111) although these results have not been confirmed by others (79, 182). More interesting is the correlation between GI symptoms and abnormal motor patterns, such as clustered activity and prolonged, progated contractions (112, 113), although others have failed to confirm this (79, 182).

In order to evaluate characteristics of individual contractions of the different phases of MMC, the spatial and temporal resolution needs to be high. Sarna and co-workers have studied this in the human jejunum (181). Our group has developed a method of evaluating the propagation pattern of individual pressure waves in the antrum and duodenum (17). With this technique, patients with chronic severe dyspepsia and IBS patients demonstrated a higher proportion of retrograde duodenal pressure waves compared with healthy subjects (20, 195), both in phase II and post-prandially.

Previous data on small intestinal motility in humans with CRF is lacking. A recent study in dogs with moderate renal failure showed altered small intestinal motility and colon transit (124). There is limited data on transit studies in CRF patients, but one study using a breath test showed prolonged transit time (58).

To conclude, there is convincing evidence of disturbed small intestinal motility in a broad range of diseases, but no uniform motility pattern has been found and a consistent correlation between motility findings and symptoms has been difficult to demonstrate. Motility studies in chronic renal failure have focused on gastric emptying and gastric myoelectrical activity. However, the small intestinal motility in patients with CRF is unexplored.

4. BACTERIAL INFECTIONS IN THE GI TRACT

4.1. Helicobacter pylori

Helicobacter pylori (Hp), a gram-negative spiral bacterium, is an important aetiological agent for gastritis, duodenitis as well as gastric and duodenal ulcers (136). In vitro studies have shown that the addition of urea to a medium containing Hp allows survival at low pH (217). Helicobacter pylori have a high urease activity that splits urea in the gastric juice into ammonia and carbon dioxide. The ammonia neutralises gastric acid in the close surroundings of the bacterium, allowing the organism to survive in the hostile environment of

the stomach. In order to achieve the diagnosis of Hp infection, microscopic examination or bacteriological culture from antral biopsies can be performed (128, 232). Two other commonly used and more rapid tests rely on the high urease activity of Hp. The urease slide test demonstrates urease activity in antral biopsies obtained at endoscopy (137) and the urea breath test, which depends on increased respiration of radio-labelled CO_2 derived from the splitting of ingested urea (48). Another non-invasive method is a serological test for Hp antibodies, used in several reports on Hp prevalence in uraemic patients (130, 151). The sensitivity and specificity for these tests varies from 80 to over 90%.

There are discordant data concerning the prevalence of Hp infection in uraemic patients. The prevalence ranges from 17 to 80% depending on the study and the method (5, 43, 74, 104, 106, 130, 149, 160, 175, 187, 222, 230). The majority of these studies have found a similar prevalence of Hp infection in patients with impaired renal function compared with a control population (43, 130, 160, 175). However, others concluded that patients with renal dysfunction suffered less often from Hp infection (104, 187). Moreover, higher prevalence rates in CRF patients compared with controls have been demonstrated in some studies (230). The discrepancies in the results of these prevalence studies may be due to different grades of uraemia, the type of dialysis, the different methods for diagnosing Hp infection and the small numbers of patients.

Studies of the relationship between GI symptoms and Hp infection in CRF have yielded different results. Luzza and co-workers found no association between Hp infection and dyspepsia in HD patients (130), whereas others have demonstrated a higher prevalence of Hp infection in CRF patients with dyspepsia (5, 43).

The influence of Hp infection on gastric emptying in CRF patients has not been studied very extensively. A study from China showed no correlation between Hp infection and delayed gastric emptying (106).

4.2. Small intestinal bacterial overgrowth

The normal bowel flora is characterised by an increasing concentration of bacteria in caudal direction. The stomach is, due to the acidity, almost sterile. The first part of the small intestine contains only small numbers of bacteria, 10^2-10^3/ml, mainly of gram-positive bacteria. The number of gram-negative bacteria is lower and strict anaerobes are rare. In the distal part of the small bowel the concentration of bacteria is higher, 10^5-10^8/ml, and the flora is similar to that of

the colon with a predominance of gram-negatives and strict anaerobes more common (192).

Small intestinal bacterial overgrowth (SIBO) is characterised by an abnormal number of bacteria in the small bowel. Diarrhoea, weight loss and anaemia are symptoms commonly seen in SIBO (117, 218) and SIBO is also a common cause of malabsorption and malnutrition (141, 211). There is no uniform definition of SIBO, but a total bacterial count in the small intestine extending 10^5 colony-forming units (CFU) per ml of aspirate is often used as a definition of SIBO. However, this definition includes otherwise healthy people with a gram-positive flora in the small intestine due to hypochlorhydria (103). Consequently, a clinically more relevant definition of SIBO is to include colonic bacteria (gram-negatives, strict anaerobes and enterococci) correlated to symptoms of SIBO (117, 211), as a conditional criteria (99).

The diagnostic tests of SIBO have been controversial. The most direct method and the considered gold standard, is culture from small bowel aspirate (176, 203). However, this method is difficult to handle both for the examiner and the patient and requires fluoroscopy to ascertain the right tube position. Furthermore, both false-negative cultures yielding overgrowth by obligate anaerobes and false-positive cultures due to oral contamination do occur (86, 211). A simpler method for diagnosing SIBO is to culture from duodenal biopsy specimens during a gastroscopy. In comparison with a culture from small bowel aspirates, this method has demonstrated both inferior and equal results (172, 203). Owing to the disadvantages of culture techniques, non-invasive methods, mainly breath tests, have been developed. The 50-gram glucose hydrogen breath test and the 1-gram ^{14}C-D-Xylose breath test are the most common tests used (115, 117). The reliability and validity of the breath tests have been questioned by several authors (172, 176) although the simplicity and the high sensitivity of the breath tests make them valuable screening tools for SIBO (205).

Bacterial overgrowth of the small intestine has been recognised in a number of diseases with an obvious structural cause (28, 63, 206). However, the predisposing condition of SIBO is quite often unclear and an association with gastrointestinal motility disturbances has been proposed. In many conditions with an increased incidence of SIBO, abnormal motility of the small intestine has been reported (99, 199, 206). The activity front of the MMC (phase III) was proposed as being "an intestinal housekeeper", with the function of clearing the small intestine of luminal contents, including bacteria, into the colon (229). Small intestinal bacterial overgrowth has been demonstrated in patients with

impaired MMC activity (102, 202, 229). There are few and conflicting data on SIBO in chronic renal failure showing both high (191) and normal (58) prevalence rates. The former using cultures of aspirate and the latter using a breath test.

In summary, there is convincing evidence for the conclusion to be drawn that impaired intestinal motility is a major pathogenic factor for intestinal bacterial overgrowth. However, SIBO is poorly investigated in CRF patients and a possible association with intestinal motility is unexplored.

5. GASTRIC ACID-SUPPRESSIVE THERAPY

5.1. Overview

Over the last three decades, important improvements in the treatment of acid-related disorders have been achieved. The detection of H_2-receptors (23) and proton pumps for regulating gastric acid secretion was a prerequisite of these advances. This discovery was followed by successful synthesis of H_2-receptor antagonists (H_2-RAs) in the early 1970s (70) and the proton pump inhibitors in the 1980s (65) in order to control gastric acid secretion. Another important finding was the importance of Helicobacter pylori infection in the pathogenesis of peptic ulcer disease (136, 221). Anti-secretory agents play an important role in the management of peptic ulcer disease, gastro-oesophageal reflux disease (GORD), and non-steroidal anti-inflammatory drugs (NSAIDs) damage. Studies of 24-hour intragastric pH, both in peptic ulcer disease and GORD with oesophagitis, have confirmed the hypothesis that the healing of damage mucosa and relief of acid-related symptoms are related to the degree and duration of acid suppression produced by the anti-secretory drugs and to the duration of treatment (12, 29). A great number of comparative clinical trials have demonstrated that PPIs provide acid suppression, ulcer and oesophagitis healing and relief of acid-related symptoms superior to antagonists H_2-RAs, especially in the treatment of oesophagitis (12, 29, 56).

5.2. H_2-receptor antagonists

This group of agents are specific antagonists that inhibit gastric acid secretion by competitively and reversibly blocking the H_2-receptors on the basolateral membrane of the parietal cell (70). Cimetidine was first introduced, followed by ranitidine, famotidine and nizatidine. The different drugs vary slightly in structure, but have the same pharmacological properties. The use of

H_2-RAs is limited by some factors. They are not able to inhibit meal-induced acid secretion and are only suitable for acid suppression during periods of basal acid secretion (22) and therefore, dosing at bedtime is recommended (76). Other restrictive factors for the use of H_2-RAs are the pharmacodynamic interaction with food (69) and the development of tolerance (tachyphylaxis) (121). Adverse reactions are rare among users of H_2-blockers. These drugs are also well tolerated in chronic renal failure, but a dose reduction is necessary since renal clearance is around 60-80% (123). Rebound acid hypersecretion is now a well-known phenomenon after treatment with H_2-receptor antagonists (158). This rebound phenomenon is present within three days of treatment and the duration is approximately one week (59). The mechanism is unknown, but hypergastrinaemia and upregulation of H_2-receptors are speculated possibilities. A recent study in healthy subjects has demonstrated a possible clinical relevance of rebound acid hypersecretion (196).

5.3. Proton pump inhibitors

Proton pump inhibitors, including omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole, are effective acid-suppressing drugs that inhibit the final common pathway for acid secretion of the parietal cell. These agents are all substituted benzimidazoles, which accumulate in the acid space of the parietal cell and convert to active sulphenamides by an acid-catalysed reaction. By covalent binding, the sulphenamides inhibit the proton pump (H+/K+ATPase) irreversibly, resulting in effective acid suppression (65). The PPIs bind only to active proton pumps inserted in the parietal cell membranes and not to inactive pumps in the cytosol (178). Therefore, after finishing PPI therapy, the recovery of acid secretion depends on the rate of de novo synthesis and the breakdown of the covalent complex. Proton pump inhibitors are well tolerated in humans and long-term use of these drugs rarely produces adverse events. However, there is a risk of gastric and small intestinal bacterial overgrowth of mostly gram-positive bacteria due to hypochlorhydria, although the clinical relevance of this is questionable (68, 122, 180). The PPIs are metabolised extensively in the liver and clinical trials have demonstrated that PPIs are safe and tolerable in end-stage renal disease (108, 118). Rebound acid hypersecretion after treatment with PPIs have been found in Hp-negative, but not Hp-positive subjects (73). This rebound phenomenon appears approximately seven days after ending medication and lasts for at least two months (72). The

clinical significance of this rebound acid hypersecretion is unexplored, but studies are in progress.

5.4. The use of acid-suppressive therapy

The use of acid-suppressing drugs has increased dramatically over the past decade, yielding both PPIs and H_2-blockers (10, 223). Consequently, the cost of these drugs has escalated dramatically and are a major part of the health care budget in many countries (83, 125, 177, 223). The effectiveness of acid-suppressive therapy in many conditions explains partly the increase in use. However, a number of studies have demonstrated an inappropriate use of acid-suppressant agents, both in hospitals (83, 153, 154, 162, 223) and in general practice (10, 80, 177).

Acid-suppressive therapy in general and PPIs in particular play an important role in the management of acid-related disorders, including peptic ulcers associated with Hp infection and NSAID use, non-Hp non-NSAID ulcers and GORD. In these conditions the indication for acid suppressant is clear. The use of anti-secretory drugs is very common in uninvestigated dyspepsia, although the value of these drugs has been controversial. Guidelines have recommended a single course of treatment with an acid-suppressant drug for 2-4 weeks in patients under 45 years without alarm symptoms (212). Endoscopy is recommended only for the elderly and patients with persistent or rapidly recurring symptoms (212). Treatment without endoscopic investigation is therefore very common in primary care (24). This empirical use of acid-suppressant medications is successful in 40-70% of patients, but the responders seem to have either GORD or peptic ulcers and the non-responders are more likely to have functional dyspepsia (138). The therapeutic gain with acid suppressants in functional dyspepsia observed in some studies is questionable due to the difficulties in excluding patients with GORD and the minimal difference in effectiveness compared with placebo.

Acid-suppressive drugs are often prescribed as ulcer prophylaxis together with the use of corticosteroids in different diseases. Whether corticosteroid therapy leads to peptic ulcer or not has been disputed for several years. In 1976, a pooled analysis by Conn and Blitzer found no association between corticosteroid use and peptic ulcers (41). A subsequent meta-analysis showed that peptic ulcer disease was present in 1.8 per cent in corticosteroid users and 0.8 per cent in controls, which was significant (144). Since then, these two groups have performed additional studies with the same conclusions (37, 42).

Piper and co-workers found a higher risk for peptic ulcers only with the combined use of corticosteroids and NSAIDs (164), which supports the findings of Conn et al.

Adverse events are very common among NSAID users and most of the side-effects are gastrointestinal, predominantly gastroduodenal ulcers, erosions and dyspeptic symptoms (30). Chronic NSAID users have a high prevalence of gastric and duodenal ulcers, with rates varying between 10 and 30% (89, 139). Proton pump inhibitors have demonstrated a prophylactic effect against ulcers and dyspeptic symptoms in the long-term use of NSAIDs (57, 140) and can be used as NSAID prophylaxis in patients with certain risk factors (120).

In summary, acid-suppressive therapy is very common and constitutes an economic encumbrance for many health care providers. An inappropriate use of these drugs is demonstrated in hospitalised patients and in primary care patients, although the use in patients with a chronic disease in general and in patients with chronic renal failure in particular, have not been explored.

6. HEALTH-RELATED QUALITY OF LIFE (HRQOL)

6.1. Overview

The measurement of health-related quality of life (HRQOL) focuses on the patient's subjective experience of the impact of disease on daily activities and well-being (13). Wider aspects of quality of life and more objective parameters of disease activity, such as symptoms and biological variables should not be included when HRQOL is evaluated. Health-related quality of life has become an important tool in assessing and explaining disease outcomes (85). There is an increasing interest in quality of life (QOL) issues in clinical research (67, 93, 96, 152). Since quality of life is perceived individually by each patient, self-administered questionnaires are preferable (14, 231). General or generic HRQOL instruments are constructed for any population, regardless of the underlying disease. Disease-specific instruments on the other hand can elicit information specific to a given disease or condition. Usually, a combination of generic and disease-specific questionnaires is used in order to cover several aspects of the impact of various diseases on HRQOL.

6.2. HRQOL in chronic renal failure

Chronic renal failure contributes to increased morbidity and mortality and has a profound impact on HRQOL (61, 90). However, there are studies in

uraemic patients demonstrating relatively high QOL (67). Patients with CRF experience several common attributes that contribute to decreased HRQOL, such as lack of energy, impairment in social life and sex life and fluid restrictions (90, 173). Factors affecting HRQOL in CRF patients include anaemia (148), decreased glomerular filtration rate (GFR) (173), gender (148, 173), nutrition (147), and depression (186). Furthermore, studies have demonstrated HRQOL to be superior in pre-dialysis patients and in transplanted patients compared with patients in dialysis (82, 186). When comparing CRF patients to those with other chronic diseases, diabetics demonstrated better HRQOL, but patients with a chronic obstructive pulmonary disease showed worse HRQOL (47).

The impact of gastrointestinal symptoms in CRF patients on HRQOL assessed by psychological well-being is up to now unexplored.

AIMS OF THE PRESENT STUDIES

The limited knowledge of the prevalence of gastrointestinal symptoms in chronic renal failure and their underlying pathophysiological mechanisms raised the following questions:

1. Do patients with CRF have an increased prevalence of GI symptoms and is there a relationship between gastrointestinal symptoms and psychological well-being?

2. On what indications do CRF patients receive acid-suppressive therapy? Is there an inappropriate use of acid-suppressive drugs among uraemic patients?

3. Do patients with CRF have disturbed small intestinal motility and are abnormal motor patterns associated with gastrointestinal symptoms in patients with CRF? Are abnormal motor patterns part of the pathophysiology behind these symptoms?

4. Does chronic renal failure predispose to small intestinal bacterial overgrowth? Are there any correlations between SIBO, small intestinal motility and GI symptoms?

5. Do CRF patients exhibit a gender-specific difference in gastric emptying compared with healthy controls? Can changes in gastric emptying explain some of gastrointestinal symptoms in CRF?

METHODS

The studies were performed according to the Declaration of Helsinki and were approved by the Göteborg University Ethics Committee. All the participants in the studies gave informed consent. The methods used are introduced and commented on in this chapter. For further details, see separate papers (I-IV).

SUBJECTS

The studies were carried out between 1999 and 2002 in patients with chronic renal failure. The definition of patients with chronic renal failure was patients in dialysis, either haemodialysis or peritoneal dialysis and predialytic patients with a GFR < 25 ml/min and/or serum-creatinine > 300 ml/l. Using this definition, the CRF patients were divided into three sub-groups for different comparisons in the studies.

Paper I

In this study, 277 patients, covering nearly all dialysis patients in the area around Göteborg and Borås, were invited to participate. Two hundred and thirty-three patients completed the questionnaires, giving a response rate of 84%. For comparison, we used the values from a previous study performed in the general population in the south of Sweden, including 2,162 healthy people (49).

Paper II

The 293 dialysis patients in the study, 202 in haemodialysis and 91 in peritoneal dialysis, were recruited from the same centres as in Paper I. Control groups consisted of 181 hospitalised patients and 261 patients with another chronic disease, either a rheumatologic or a pulmonary disease. The dominating disease among the rheumatologic patients and pulmonary disease patients were rheumatoid arthritis (60/84, 70%) and chronic obstructive pulmonary disease (46/94, 49%) respectively. All these control patients were recruited from the community hospital in Borås. The hospitalised patients were admitted consecutively to two internal medicine wards and the patients with a rheumatologic or pulmonary disease were recruited from two out-patient clinics.

Paper III

In this manometry study, 22 patients with CRF, 12 with GI symptoms and 10 without GI symptoms, were investigated. The results were compared with 34 healthy subjects without GI symptoms, of whom thirty-two were historical controls from a previous study conducted by our group (195). The

Gastrointestinal Symptom Rating Scale (GSRS), a self-administered questionnaire, was used to assess the presence and severity of GI symptoms. In this instrument, data is presented as syndrome scores and a total score. The lowest possible score is 1.00 and the higher the scores the more pronounced the symptoms. Reference values were obtained from the previous study, used in Paper I, with a total GI symptom score of 1.53 (1.50-1.55) (49). Cut-off levels for symptomatic CRF patients were a total GI symptom score above 2.0 or at least two syndrome scores above 2.0. Organic GI disorders were excluded by conventional investigations, including stool culture, endoscopy and laboratory parameters.

Comments. The cut-off levels for dividing patients into a symptomatic and an asymptomatic group were chosen arbitrarily and there is no natural limit at 2.0. To our knowledge, no specific score level for GI symptoms has been applied in previous studies. However, we assumed that these levels were reasonable, since they had been chosen according to levels in the general population.

Paper IV

The gastric emptying study included 39 patients with CRF, 18 with GI symptoms and 21 without GI symptoms. Gastric emptying results were compared with reference values from our laboratory, obtained in 131 healthy subjects. The separation of CRF patients into symptomatic and asymptomatic groups and the way of excluding gastrointestinal disorders in these patients were the same as in Paper III. The upper reference value for the gastric emptying rate (the 95th percentile) was calculated from the data of healthy controls.

QUESTIONNAIRES (I, III, IV)

Two types of self-administered questionnaires were used in the studies in order to assess GI symptoms (I, III, IV) and psychological well-being (I). The results were compared between the sub-groups within the CRF patients (I) and with results recently obtained in other disease groups (193, 194) and normal values from the general population (49). In Paper I, correlations between psychometric scores and severity of subjective GI symptoms were assessed. As mentioned, above, the GSRS was used in Papers III and IV to obtain GI symptom levels. The two questionnaires are summarised in Table 1.

Gastrointestinal Symptom Rating Scale (GSRS) (I, III, IV). The GSRS was originally constructed as an interview-based rating scale designed to evaluate a wide range of gastrointestinal symptoms (208) and was later modified

to become a self-administered questionnaire (50). The questionnaire includes 15 items and uses a 7-grade Likert scale defined by descriptive anchors. The higher the scores, the more pronounced the symptoms. The following five dimensions were identified on the basis of a factor analysis (51) and were used in this study: Abdominal Pain Syndrome (three items), Reflux Syndrome (two items), Indigestion Syndrome (four items), Diarrhoea Syndrome (three items), and Constipation Syndrome (three items). One item, Eating Dysfunction, previously developed in a manner analogous to the GSRS (209), was also considered clinically relevant and modified to become self-administered for this study. The GSRS data are presented in syndrome scores, a total score and a separate score for Eating Dysfunction.

Psychological General Well-Being (PGWB) Index (I). The PGWB index was developed for the purpose of providing a self-reporting instrument that could be used to measure subjective well-being or distress (234). Extensive documentation with regard to reliability and validity is available for the questionnaire (93, 96, 152, 224). The PGWB includes 22 items, divided into six dimensions: Anxiety (five items), Depressed mood (three items), Positive well-being (four items), Self-control (three items), General health (three items), and Vitality (four items). These items are also combined into a global overall score. The sub-scales used to measure these six states thus have three to five items, each using a 6-grade Likert scale. Scores are calculated for each dimension and for an overall PGWB index, with higher scores indicating greater well-being.

Comments. Health-related QOL, one part of QOL, is the way disease, positively and negatively, influences daily life. Hjortswang and co-workers have developed a strategy to describe health by using the following five variables; biological variables, symptom burden, disease-related worry, function and general well-being (95). The use of GSRS and PGWB in our study does not give a complete description of HRQOL according to this strategy, since the instruments used do not cover all dimensions. As mentioned earlier, it is considered of vital importance that the patients are the primary source of HRQOL (14, 231). This approach to evaluate psychological well-being was adopted here, using two different self-administered questionnaires.

Table 1. Questionnaires used in this thesis. Tabled according to Hjortswang (94)

Questionnaire Dimensions	Items	Scale	Contents
PGWB	32	Likert (1-6)	
Anxiety	5		Feeling nervous, tense, anxious, worried, under stress, relaxed
Depressed mood	3		Feeling sad, discouraged and hopeless, downhearted and blue
Positive well-being	4		Feeling happy, satisfied with personal life, cheerful
Self-control	3		Feeling emotionally stable, self-assured, afraid of losing control
General health	3		Bothered by illness, body disorders, pain, worried about health
Vitality	4		Feeling tired, worn out, feeling active versus dull
GSRS		Likert (1-7)	
Reflux	2		Acid regurgitation, heartburn
Abdominal pain	3		Abdominal pain, sucking sensation in the epigastrium, nausea and vomiting
Indigestion	4		Borborygmus, abdominal distention, eructation, increased flatus
Constipation	3		Decreased passage of stool, hard stools, feeling of incomplete evacuation
Diarrhea	3		Increased passage of stool, loose stools, urgent need for defaecation
Separate item			
Eating dysfunction	1		Early satiety, difficulties in eating normal portions, post-prandial pain

MANOMETRY RECORDINGS (III)

Antroduodenojejunal manometry was performed after an overnight fast, using a water-perfused (0.3 ml/min) eight-channel catheter for pressure recording (Zinetics, Salt Lake City, Utah, USA). The catheter was connected to pressure transducers and recordings were made with a polygraph (PC Polygraph, Synectics, Stockholm, Sweden), which converted the obtained pressure data into digital information at 4 Hz. The individual registration was displayed on the computer screen during recording and stored for later analysis. Under fluoroscopic guidance, the catheter was placed with its tip in the proximal part of jejunum. The pressure recording side holes were situated 2, 17, 30, 32, 34, 45.5, 47 and 48.5 cm from the tip of the catheter. Three ports were thus situated in the antrum 1.5 cm apart (A_{1-3}), three in the descending part of the duodenum 2 cm apart (D_{1-3}), one in the distal duodenum, close to the ligament of Treitz (T), and one in the proximal jejunum (J) (Figure 1).

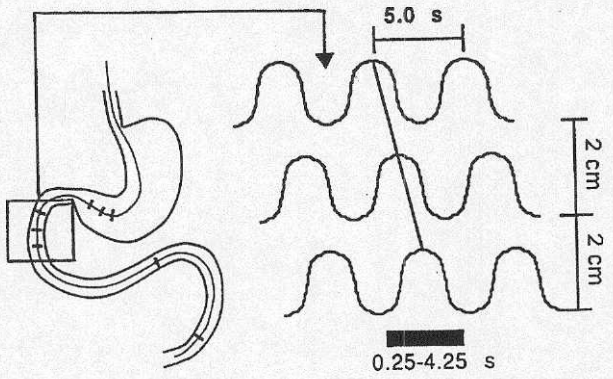

Figure 1. Schematic presentation of the catheter, with recording points in the antrum (A_{1-3}), proximal duodenum (D_{1-3}), distal duodenum (T) and jejunum (J) and the time window criteria used for the analysis of propagated pressure waves in the 4-cm segment of the proximal duodenum, with a maximal frequency of 12 contractions/min (17)

Figure 2. Conventional manometry recording in a CRF patient with gastrointestinal symptoms, demonstrating a high number of long clusters

The participants sat as comfortably as possible in a semi-reclining position during the recordings. Fasting (interdigestive) motility was recorded for five hours. Post-prandial motility was then recorded for one hour after a standard meal consisting of porridge, milk and white bread with butter and cheese (500 kcal).

ANALYSIS OF MANOMETRY DATA (III)

Conventional evaluation of the condensed manometry data was performed by one of the investigators (M.S.), who was blinded to the clinical characteristics of the patients (Figure 2). Motor abnormalities of the small intestine were divided into either neuropathic-like (normal amplitudes but an abnormal contraction pattern) or myopathic-like patterns (persistently low contraction amplitude). An analysis of different motility variables was evaluated by direct visual inspection on the computer screen and using a commercially available computer program (Table 2) (Polygram version 5.06 X1, Synetics Medical, Stockholm, Sweden). A long cluster (burst) of intestinal activity was defined as a sequence of pressure waves at the maximal contractile activity (10-14/min), lasting for ≥30 seconds, and preceded and followed by motor quiescence but not followed by motor phase I-like quiescence. In order to analyse the propagation pattern of individual pressure waves in the antrum and the proximal duodenum, assessment with high temporospatial resolution was performed. The number and the propagation direction (antegrade versus retrograde) of these pressure waves were determined. The direction of propagation was determined visually on the computer screen, and confirmed by the automated computerised analysis, with positive and negative velocity indicating antegrade peristalsis and retrograde peristalsis.

Comments. Antroduodenojejunal manometry has not been performed previously in patients with chronic renal failure. The large inter- and intra-individual variations in manometry findings in humans make individual interpretations of motor abnormalities in the small intestine difficult. However, manometry recordings from a larger group, i.e. the CRF patients in Paper III, might demonstrate a common abnormal motor pattern, partly explaining GI symptoms in these patients.

To evaluate the propagation pattern, time window criteria were used (17) (Figure 1). The time window chosen for analysis of propagation along a 4 cm-segment was 0.25-4.25 seconds, which allowed calculation of individual pressure waves with the velocity between 0.9 and 16 cm/s in phases II and III in

both the antegrade and retrograde direction. This way of measuring pressure waves has been validated previously (19)

GASTRIC EMPTYING TEST (IV)

After an overnight fast, the patients had a standardised breakfast consisting of oatmeal porridge and one cheese sandwich (400 kcal). Twenty spherical radiopaque markers (ROMs) were added to the meal. After four hours the first fluoroscopic control was accomplished. Fluoroscopy was then repeated at five hours and six hours, unless all the markers had disappeared from the stomach. The individual mean gastric retention of markers four to six hours after the meal was calculated and used as a measure of gastric emptying. Since a gender difference has been demonstrated (179, 204), men and women were compared separately.

Comments. The simplified technique, starting fluoroscopic controls four hours after ingestion of markers, creates both advantages and disadvantages. This is easier, safer and less time-consuming, both for patients and investigators. However, the method is limited, since only delayed gastric emptying can be evaluated. Nevertheless, the previous measurement of gastric emptying in chronic renal has found a relationship between GI symptoms and delayed gastric emptying but no relationship with the rapid gastric emptying rate.

Table 2. Important manometry variables analysed in Paper III. The periods during which these variables were assessed and the segments, as well as the units of the variables, are also shown

Manometry variable	Unit	Period	Segment
Phase III	Number/ 5hrs	5 hrs, fasting	A1-3, D1-3, T, J
Long cluster	Number / 5hrs	5 hrs, fasting	D2, T, J
Individual pressure waves	Number / 30 min	Late phase II (30 min)	A2-3, D1-3
		Post-prandially (30 min)	D1-3
Retrograde pressure waves	% of all propagated waves	Late phase II (30 min)	A2-3, D1-3
		Phase III (last min)	D1-3
		Post-prandially (30 min)	D1-3
Propagation velocity (phase III)	cm/min	5 hr fasting	D1-3, D3-J

TEST FOR SMALL INTESTINAL BACTERIAL OVERGROWTH (III)

After an overnight fast, patients arrived at the laboratory for an antroduodenojejunal manometry. Under fluoroscopic guidance, the tip of the manometry catheter was placed in the proximal part of jejunum. At the end of the manometry recordings an aspirate from the jejunum was obtained and collected in a sterile tube. Within two hours, specimens were cultured for aerobic bacteria, anaerobic bacteria and yeast fungus, with a minimum incubation time of 48 hours. Quantification was performed by counting the number of colony-forming units (cfu) and the jejunal aspirate was considered positive if the total count of colonic type bacteria was > 10^5 cfu/ml.

Comments. Breath tests are easy to perform and are widely used. However, these tests have low specificity and sensitivity and were therefore avoided. The risk of a false positive culture due to contamination is believed to be common in the use of open tubes. However, these have been proven to be as good as closed systems (159, 211). The anaerobic conditions during the sampling and transporting procedures could be problematic. However, the upper part of the small bowel is regularly exposed to swallowed air and the bacteria living in this environment are mostly not strictly anaerobic. Furthermore, fresh aspirate is known to tolerate oxygen exposure well for at least eight hours (213).

TEST FOR HELICOBACTER PYLORI INFECTION (IV)

A serum sample was obtained for the assessment of Hp antibodies (IgM, IgG) by an enzyme-linked immunoadsorbent assay. The method, an in-house diffusion-in-gel ELISA, is reliable and well validated (207).

Comments. Serological tests for Hp infection have a somewhat lower sensitivity compared with the urea breath test (UBT), antral biopsies for urease test (CLO test) and histology, but a good positive predictive value (62, 175).

DATA COLLECTION (I, II)

In Paper I, the following data were collected from medical records: underlying renal disease, height, weight, s-urea, s-albumin, duration of dialysis, dialysis efficacy (K_t/V), and drugs used for GI disorders/symptoms. Height and weight were used for the calculation of body mass index (BMI). Information about acid-suppressive therapy and history of endoscopic evaluation in Paper II

were obtained by interviewing the patients and in some cases also by reviewing medical records.

STATISTICAL METHODS

Since the results of the questionnaires and the investigations do not follow a normal distribution, non-parametric tests were mainly used. Results are mostly presented as median and interquartile range (IQR) (I, II, III, IV) except when GSRS data are compared with results from another study population, where mean and standard error of the mean (SEM) (I, III, IV) are used. In general, significance was accepted at the 0.05 level.

The *Mann-Whitney U-test* was used for a comparison of continuous and ordinal data in two-sample cases (I, III, IV)

The *Kruskal-Wallis test* was used for a comparison of continuous and ordinal data between more than two groups. If significant, a post hoc analysis using the Mann-Whitney U test was performed (I, III)

Chi-square test (Fisher's exact test) was used for a comparison of nominal data (II, III, IV).

Correlations between continuous/ordinal data were analysed by the *Spearman rank order correlation coefficient* (Rho) (I, III).

Multiple stepwise logistic regression was used to examine the relationship between one dependent variable with one or more independent variables (I).

In Paper IV, the 95th percentile of the gastric emptying rate in the healthy controls was assessed to serve as a reference limit.

RESULTS AND COMMENTS

GASTROINTESTINAL SYMPTOMS AND HRQOL (I)

All three CRF patient groups had a higher prevalence of gastrointestinal symptoms compared with controls, demonstrated as a significantly higher mean total GSRS score (Table 3). This also applied to all GSRS domains, except for reflux, where only PD patients demonstrated higher scores than the reference values (Table 3). Patients in peritoneal dialysis had more gastrooesophageal reflux and eating dysfunction compared with haemodialysis patients and predialytic patients ($p<0.01$). Multivariate analysis showed that these differences were not related to a higher proportion of diabetic patients in the PD group. Diabetes mellitus had limited impact on GI symptoms. Patients with diabetic nephropathy only scored higher in the single item, eating dysfunction (data not shown). Serum-albumin correlated negatively with eating dysfunction (Rho = -0.33, $p<0.01$). The duration of dialysis and age had no influence on GI symptoms.

A relationship between GI symptoms and HRQOL was indicated by the negative correlation between the GSRS total symptom score and the total PGWB index (Rho = -0.46, $p<0.001$). Haemodialysis patients demonstrated significantly reduced psychological well-being compared with the general population and predialytic patients, especially for the PGWB dimensions; positive well-being, general health and vitality (Table 4). In general health and vitality, PD patients and predialytic patients also had lower scores than the controls, but otherwise there were no other differences (Table 4). Patients with diabetic nephropathy had lower psychological well-being than the other CRF patients ($p<0.05$).

Table 3. GSRS scores in CRF patients and in the control population.

GSRS	HD patients (N = 127)	PD patients (N = 55)	Predialytic patients (N = 50)	Control population (N = 2162)
Total	2.14 (2.05-2.23)**	2.24 (2.12-2.36)**	2.03 (1.93-2.13)**	1.53 (1.50-1.55)
Reflux	1.44 (1.36-1.52)	1.88 (1.71-1.95)*	1.33 (1.23-1.44)	1.56 (1.53-1.59)
Abdominal pain	1.97 (1.87-2.07)**	2.23 (2.07-2.39)**	1.86 (1.72-2.00)*	1.78 (1.75-1.82)
Constipation	2.23 (2.11-2.35)**	2.04 (1.88-2.20)*	1.92 (1.76-2.08)*	1.39 (1.36-1.43)
Indigestion	2.41 (2.30-2.52)**	2.36 (2.21-2.51)**	2.34 (2.18-2.50)**	1.55 (1.51-1.58)
Diarrhoea	2.26 (2.12-2.40)**	2.56 (2.33-2.79)**	2.38 (2.17-2.59)**	1.38 (1.35-1.41)

.* = $p<0.05$, compared with the control population
** = $p<0.001$, compared with the control population

Table 4. PGWB scores in CRF patients and the control population.

PGWB	HD patients (N = 127)	PD patients (N = 55)	Predialytic patients (N = 50)	Control population (N = 2162)
Total	91.4 (89.5-92.3)[a, c]	95.6 (93.0-98.2)[b]	100.1 (97.8-102.4)	102.9 (102.1-103.8)
Anxiety	23.3 (22.8-23.8)	24.1 (23.5-24.7)	25.3 (24.7-25.9)	24.1 (23.8-24.3)
Depressed mood	14.2 (13.9-14.5)[a]	14.9 (14.5-15.3)	15.3 (14.9-15.7)	15.5 (15.4-15.6)
Positive well-being	13.7 (13.3-14.1)[a, c]	14.9 (14.3-15.5)[b]	15.4 (14.9-15.9)	16.1 (15.9-16.3)
Self-control	14.3 (14.0-14.6)[a]	14.7 (14.3-15.1)	15.3 (15.0-15.6)	15.3 (15.2-15.4)
General health	11.9 (11.6-12.2)[a, c]	12.4 (12.0-12.8)[a]	13.3 (12.9-13.7)[a]	14.6 (14.5-14.7)
Vitality	13.9 (13.5-14.3)[a, c]	14.6 (14.0-15.2)[a]	15.5 (15.0-16.0)[a]	17.2 (17.0-17.4)

[a] $p<0.001$ compared with the control population.
[b] $p<0.05$ compared with the control population
[c] $p<0.05$ compared with predialytic patients

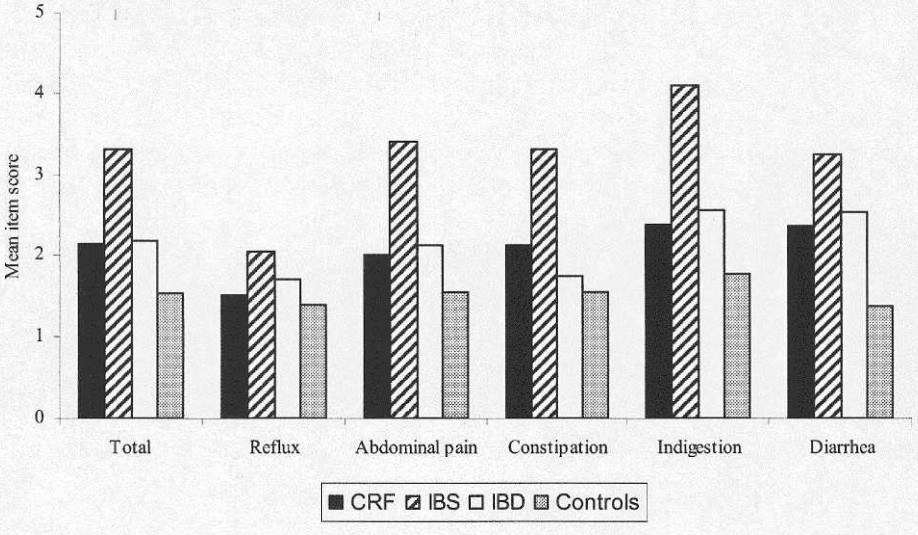

Figure 3. The severity of GI symptoms measured using GSRS. The symptom scores of CRF patients are compared with previous scores achieved in patients with irritable bowel syndrome (IBS) (193), inflammatory bowel disease (IBD) in remission (194) and with reference values from a population in the south of Sweden (49).

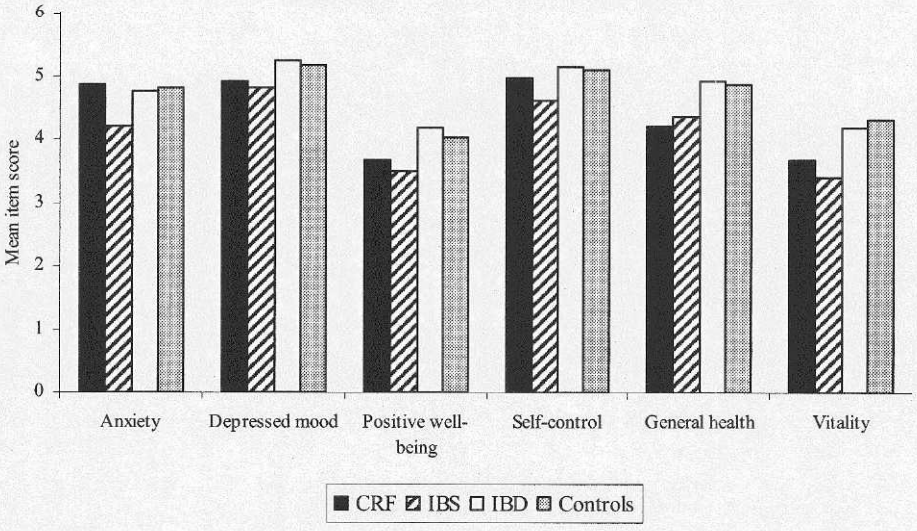

Figure 4. Psychological well-being measured using the PGWB index. Results from CRF patients in the present study compared with previous scores achieved in patients with irritable bowel syndrome (IBS) (193), inflammatory bowel disease (IBD) in remission (194) and with reference values from a population in the south of Sweden (49).

In Figures 3 and 4, comparisons of GSRS scores and PGWB scores with other disease groups recently studied by our group, are shown respectively. The gastrointestinal symptoms measured by GSRS were equal in CRF patients and patients with an inflammatory bowel disease (IBD) in remission, but higher in IBS patients. The psychological general well-being was reduced both in IBS and CRF patients, while IBD patients in remission were comparable to the general population.

Differences in the GSRS and the PGWB scores between sub-groups of CRF will be presented and discussed below.

Comments. The fact that the reference values were taken from another study might lead to differences in age and gender as well as racial group. The CRF patients were older than the reference group, but the results in the survey from the general population in the age group 50-60 and 60-70 were not significantly different from the total group, neither in the GSRS nor the PGWB index. Furthermore, 95% of our patients and the control group were of Caucasian origin.

USE OF ACID-SUPPRESSIVE THERAPY (II)

Comparisons with other patient groups (II)

The dominating drugs were PPIs, used by 93% of patients receiving acid-suppressive therapy. The use of acid-suppressive drugs among the three groups in the study is shown in Figure 5 together with the results from a recent study performed by our group showing a similar high use of these drugs in hospitalised patients. Dialysis patients exhibited a higher consumption compared with hospitalised patients, but not higher than patients with another chronic disease. However, when splitting the groups into sub-groups, dialysis patients had a higher use compared with patients with a chronic pulmonary disease (41% vs 16 %, $p<0.001$), but not compared with rheumatologic patients (41% vs 34%, NS). A recent study from our group has shown a similarly high consumption of PPIs and H_2-blockers among hospitalised patients in a pulmonary ward (49%) and in a surgical ward 49% (157) compared with CRF patients. Haemodialysis patients and PD patients consumed acid-suppressive medication to the same extent and the inappropriate use of these drugs was equal. However, reflux disease was a more common indication for acid-suppressive drugs in PD patients compared with HD patients ($p=0.056$).

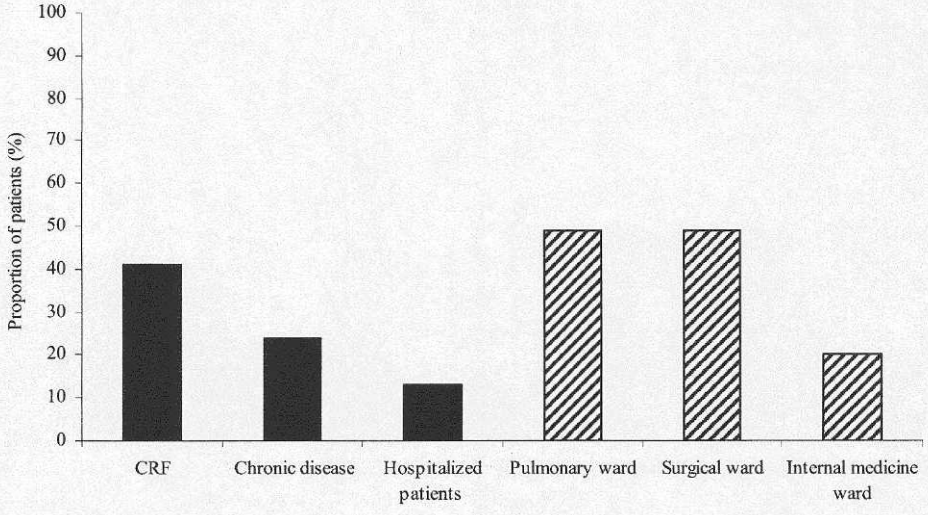

Figure 5. The use of acid-suppressive therapy in the present study compared with another study from our group performed in another population (157). The majority of our patients came from a community hospital and from dialysis units **(black bars)**, while the other study was carried out in a university hospital **(striped bars)**

Duration of acid-suppressive therapy (II)

Long-term treatment, defined as use of acid-suppressive therapy for eight weeks or longer, was common in all the three groups, with very high rates in CRF patients (77%) and in patients with another chronic disease (84%).

Comments. The limit for long-term use was chosen arbitrarily. However, one of the longest non-maintenance therapies is the healing of reflux oesophagitis, which has a recommended treatment period of four to eight weeks.

Indication for therapy (II)

Inadequate indications dominated in the CRF patients (63%) and the hospitalised patients (81%). The majority of indications in the patients with another chronic disease were appropriate (68%). The indications for acid-suppressive therapy and their frequency for all patients in Paper II are listed in Table 5, with adequate and inadequate indications in different columns. The most common adequate indication in CRF was GORD (28% of total indications), whereas dyspepsia, including abdominal pain, was the most inadequate indication (25% of total indications).

Comments. The decision whether the use of a drug is appropriate or not varies over time depending on many factors. We used the current definition of adequate indications supported by the medical literature.

Table 5. Indications for acid-suppressive therapy (AST) in the 199 patients.

Reason for AST	Adequate indication Proportion (%)	Inadequate indication Proportion (%)
GORD	22	
Dyspepsia		16
Corticosteroid prophylaxis		12
NSAID prophylaxis	11.5	
No reason found		10
Peptic ulcer[a]		8
Abdominal pain		6.5
Other[b]		6.5
Peptic ulcer	4.5	
Upper GI bleeding	2.5	
Lower GI bleeding		1

a. Previous peptic ulcer not followed by OGD and Hp-test
b. Nausea, vomiting, and anaemia.

Endoscopic evaluation (II)

Oesophagogastroduodenoscopy (OGD) had been performed in 42% of the patients on acid-suppressive therapy with similar values in CRF patients (42%), hospitalised patients (46%) and in patients with another chronic disease (41%).

VISCERAL MOTILITY (III, IV)

Antroduodenojejunal manometry (III)

Abnormal motility pattern was observed in 50% (11/22) of the CRF patients and all of these were neuropathic-like abnormalities. The number of activity fronts (phase III) during fasting recording did not differ between the groups, although antral phase III was recorded in a significantly lower proportion of CRF patients compared with healthy controls (16% vs 53%, $p<0.016$). The proportion of retrograde pressure waves in late phase III (last minute) was high in both patients and healthy controls, without any significant difference (90% (28-90) vs 100(60-100), $p=0.07$).

In phase II, a higher number of long clusters was observed in CRF patients compared with the controls (10(6-18)/5 hrs vs 4(1-9)/5 hrs, $p=0.0016$). Another motor abnormality observed in phase II and post-prandially, was a higher proportion of retrograde pressure waves in CRF patients compared with healthy controls (Table 6). The number of propagated contractions 30 minutes after the meal was higher in CRF patients compared with healthy subjects (14(9-23) vs 10(6-16), $p=0.024$).

The proportion of patients in the different sub-groups of CRF did not differ in Paper III. However, the number of patients in each sub-group was too small for adequate comparisons to be made between them.

Comments. The dominance of retrograde pressure waves in late phase III seen in both healthy subjects and CRF patients has also been demonstrated in functional bowel disorders as well as in metabolic and pharmacological interventions and is probably part of the normal physiology of the MMC (18, 20, 21, 195).

Gastric emptying (IV)

Male CRF patients had a significantly higher mean gastric retention 4-6 hours after the meal compared with healthy men (16.6(0-63.3)% vs 0(0-2.1)%, $p<0.0001$. In women, there was no significant difference in gastric retention between CRF patients and healthy controls. The 95th percentile of mean gastric retention variable in the healthy controls was assessed to serve as a reference limit for delayed gastric emptying. Using these reference values, a high proportion of CRF patients revealed a marked delay in gastric emptying, both in men (10 of 22, $p<0.0001$) and women (4 of 17, $p<0.02$). In line with previous studies, age had no influence on gastric emptying. Delayed gastric emptying was more common in PD patients compared with predialytic patients (6 of 9 vs 2 of 13, $p=0.026$), but not compared with HD patients (6 of 9 vs 6 of 17, $p=0.22$) (IV).

Comments. Scintigraphy is considered to be the gold standard for measuring gastric emptying of digestible solids and liquid. However, this method has the disadvantages described above. Radiopaque markers for the assessment of gastric emptying of indigestible solids have demonstrated a high degree of correlation with the scintigraphic methods (204) and was therefore used in Paper IV.

Table 6. The proportion of retrograde pressure waves in the proximal duodenum in phase II and post-prandially in CRF patients and healthy subjects.

Subjects	Proportion of retrograde pressure waves in the prox. Duodenum	
	Late phase II (%)	Post-prandially (%)
CRF patients with GI symptoms	33(24-50)[a]	29(17-38)[a]
CRF patients without GI symptoms	23(17-33)[a]	16(14-42)[b]
Healthy subjects	0(0-13)	8(0-24)

[a] $p < 0.001$ compared with healthy subjects
[b] $p = 0.07$ compared with healthy subjects

BACTERIAL INFECTIONS IN THE GI TRACT (III, IV)

Helicobacter pylori (IV)

In the gastric emptying study (IV), eight of the 31 (26%) patients with CRF were Hp positive with a serologic test. There was no difference in the prevalence of Hp infection between symptomatic and asymptomatic patients (31% vs 22%, N.S.). Moreover, mean gastric retention 4-6 hrs after the meal did not differ between Hp positive and Hp negative CRF patients 16.6 (5.8-59.1)% vs 13.3 (0-64.6), p=0.75).

Small intestinal bacterial overgrowth (III)

Culture of jejunal aspirate revealed bacterial overgrowth in eight of the 22 CRF patients (36%) with no difference between patients with and without symptoms. Two colonic bacterial strains dominated, Escherichia coli and Enterobacter, both occurring in three patients. The patients with SIBO exhibited somewhat more abnormal motility patterns. Lack of phase III activity in the small intestine was more common in CRF patients with bacterial overgrowth than CRF patients without SIBO (3 of 8 vs 0 of 14, p=0.036). However, no difference in antral phase III activity was seen in these two groups (p=0.77). Furthermore, CRF patients with a neuropathic-like motility pattern had a tendency towards higher prevalence of SIBO compared with patients without a neuropathic-like motility pattern (6/11 (55%) vs 2/11 (18%), p=0.07).

Comments. The small sub-groups in Paper III can lead to type II errors and the interpretation of the comparisons between these groups must be done with caution.

GASTROINTESTINAL SYMPTOMS AND PATHOPHYSIOLOGY (II, III, IV)

Patients in Paper I taking PPIs demonstrated higher GSRS scores than the rest of the patients, especially for abdominal pain (2.33 (1.33-3.67) vs 1.33 (1.00-2.00), $p<0.0001$) and eating dysfunction (2.00 (1.00-4.00) vs 1.00 (1.00-2.00), $p<0.001$) (I).

The propagation velocity of phase III in the duodenum in the symptomatic CRF patients was significantly higher than the velocity in the CRF patients without GI symptoms and the healthy subjects (Table 7). Moreover, a relationship between propagation velocity of phase III in the duodenum and the GSRS score diarrhoea among CRF patients was observed (Rho=0.57, p=0.028). Other abnormal motility patterns found in CRF patients compared with healthy controls were not different between CRF patients with and without GI symptoms (III).

Delayed gastric emptying in CRF patients, particularly in men, was not associated with the presence of GI symptoms (men with and without GI symptoms: 13.3 (0-55.0)% vs 47.5 (5.0-65.0)%, p=0.51, women with and without GI symptoms: 16.6 (0-51.7)% vs 13.3 (0-59.2)%, p=0.96) (IV)

Comments. The difficulty finding a relationship between GI symptoms and pathological small intestine motility and gastric emptying in uraemic patients is in line with other studies (106). This is also valid for patients with functional dyspepsia and IBS (142, 143).

Table 7. Propagation velocity of phase III in CRF patients and healthy controls in cm/min

Subjects	Proximal duodenum to distal duodenum	Distal duodenum to jejunum
CRF patients with GI symptoms	21.4 (16.4-54.8) [a, b]	18.2 (10.8-34.2) [a, b]
CRF patients without GI symptoms	8.1 (4.6-9.6)	6.2 (4.2-9.6)
Healthy controls	10.8 (7.2-21.6)	9.9 (6.3-15.3)

[a] $p< 0.05$ compared with healthy controls
[b] $p< 0.01$ compared with CRF patients without GI symptoms

GENERAL DISCUSSION

The main results in the present studies will be combined and discussed briefly below and compared with other findings in the literature.

GASTROINTESTINAL SYMPTOMS AND HRQOL

The CRF patients in the present study demonstrated a high prevalence of GI symptoms indicated as high symptom scores. Elevated scores compared with controls were observed in almost all the GI symptoms studied. These data are in line with other studies (1, 5, 87, 130, 156, 226) that have demonstrated a prevalence of GI symptoms, ranging from 32% to almost 80% among uraemic patients. However, the measurement instruments used in previous studies are not very well described and there is no grading of symptoms. In the present study, the use of a validated and reliable questionnaire (the GSRS) made the assessment of GI symptoms more reliable. Furthermore, comparisons with healthy controls and other disease groups are lacking in previous studies (1, 5, 87, 130, 156, 226). The results in our study were compared with reference values obtained in a previous general population study from the south of Sweden (49). However, a better approach in our study would have been prospectively recruited control groups, consisting of both healthy subjects and patients with another chronic disease. Factors in connection with a chronic disease, including a high consumption of drugs, the patient's distress from a chronic disease or the influence of the disease on the GI tract, could have an impact on GI symptoms in patients with CRF. Apart from the lack of control groups, another disadvantage in previous studies is that they have been conducted mostly in HD patients. We performed our study in dialysis (PD, HD) patients as well as in predialytic patients and found a similar high prevalence of GI symptoms in all three groups.

No major differences in the prevalence of GI symptoms were observed between patients with and without diabetes nephropathy. This finding was somewhat unexpected, since there is a well-known association between diabetes mellitus and gastroparesis (97). Only in the eating dysfunction item did diabetic patients exhibit significantly higher scores compared with non-diabetics. However, eating dysfunction is a question concerning early satiety and post-

prandial pain and these symptoms are also common in patients with gastroparesis, although some patients with gastroparesis are asymptomatic.

Malnutrition is a common finding in CRF (15, 39, 134, 216, 235, 237) and is an important determinant of morbidity and mortality (2, 129, 133, 200). Gastrointestinal symptoms are considered to be one of many possible factors behind malnutrition in these patients. Paper I showed that patients with low s-albumin had significantly more meal-related symptoms, indicating a plausible relationship between GI symptoms and malnutrition.

Nutrition/malnutrition is considered to be one of the disease-related factors affecting HRQOL (147). Other common factors are anaemia (148), decreased GFR (173), gender (148, 173) and depression (184). However, the impact of GI symptoms on HRQOL in uraemic patients has not been investigated very much. The negative relationship between GSRS scores and the psychological general well-being index demonstrated by us (I) indicates that GI symptoms probably have a major influence on daily life for patients with CRF. In agreement with our results, Rocco and co-workers found that bloating contributed to decreased HRQOL (173). The finding in the present study, that patients with diabetic nephropathy had a lower psychological well-being compared with the other CRF patients, is in agreement with other studies demonstrating lower HRQOL in diabetics compared with uraemic patients (155).

USE OF ACID-SUPPRESSIVE THERAPY

We demonstrated a very high consumption of acid suppressive drugs, especially PPIs, in CRF patients undergoing dialysis. This is to our knowledge the first study in uraemic patients investigating the use of these drugs. There is also limited data on patients with other chronic diseases. However, a recent study from our group has found a similar high use of PPIs in hospitalised patients with pulmonary diseases and hospitalised patients in a surgical ward (157). An overuse of acid-suppressant drugs has been described by others, but these studies have been performed either in general practice settings (10, 80, 177) or in hospitalised patients in general (83, 153, 154, 162, 223). In Paper II and in another study from our group (157), the use of these drugs in hospitalised patients in an ordinary internal medicine ward was significantly lower compared with the use in hospitalised patients performed by other groups (83, 153, 162, 223). A reason for this difference could be the allocation of patients to different

wards with the more critically ill patients in the studies, where there is a higher consumption of acid-suppressive drugs. Another possible explanation is the variation in the management of patients in hospital care in different countries.

The level of inappropriate use of acid-suppressive drugs in CRF was very high in the present study. In the majority of previous studies, both in hospitalised patients and in patients in general practice, a similar high level of inadequate use of these drugs has been demonstrated, with values ranging from 40% to 72% (83, 153, 154, 162, 177, 223). Non-specific symptoms, such as dyspepsia and abdominal pain, were common inadequate indications among CRF patients and the hospitalised patients. These findings are consistent with the results from the recent study from our group (157) and from previous reports (10, 177). The high prevalence of these indications reflects the widespread use of these expensive drugs based on poor clinical management.

One of the most frequent reasons for using acid-suppressive drugs in the majority of studies in hospitalised patients, is peptic ulcer prophylaxis with concomitant use of NSAIDs, steroids or anticoagulants in order to protect the gastroduodenal mucosa (83, 153, 162, 223). Proton pump inhibitors have demonstrated prophylactic efficacy in the use of NSAID and PPIs are therefore considered to be an adequate indication for prophylactic treatment (57). However, not all NSAID users need prophylactic treatment with PPIs. In a meta-analysis by Kurata and Nogawa certain risk factors for the development of peptic ulcers were identified, such as previous ulcers, old age, concomitant anticoagulant therapy and concomitant corticosteroid treatment (120). NSAID prophylaxis was a common indication in rheumatic patients in our study and was considered appropriate in these patients. However, we did not take into consideration the risk factors mentioned above, which might have led to an overestimation of adequate indications in this patient group. The major part of the unnecessary acid-suppressive therapy in hospitalised patients in previous studies was for prophylactic treatment, due mainly to concomitant use of NSAIDs, corticosteroids and anticoagulants (ASA), but also as stress-ulcer prophylaxis (83, 153, 162, 223). The NSAID users in these studies were mainly categorised as low-risk patients and the acid-suppressive therapy was considered unnecessary. The use of NSAIDs in chronic renal failure is limited due to the nephrotoxicity of these drugs.

The association between corticosteroid therapy and the development of peptic ulcers was previously controversial (41, 144). However, it has now been established that corticosteroids do not increase the risk of peptic ulcers (6, 42).

Only concomitant treatment with NSAIDs and high doses of corticosteroids in high-risk patients increase the risk of peptic ulcers (164). Despite this fact, corticosteroid prophylaxis was common in all groups in the present study (II), in particular among patients with a pulmonary disease. Other investigators, including a recent study from our group, have made the same observations (83, 153, 157). These findings led us to the conclusion, that "the long-living steroid ulcer myth" is still current.

In our study peptic ulcer was a rather uncommon indication in uraemic patients and all of these ulcers were verified by gastroscopy. Endoscopic lesions in the upper GI tract (145, 149, 198), but not peptic ulcers, have been found to be more common in CRF patients compared with patients with normal renal function (4, 7, 145). Peptic ulcers confirmed by endoscopy or relapsing duodenal ulcer diagnosed by urea breath tests are clear indications for acid-suppressive therapy. However, the majority of the CRF patients, with a peptic ulcer as an indication, had been on long-term therapy without any re-investigation with endoscopy or Hp testing before continuing the acid-suppressive drugs. Similar results have been shown both in general practice and in hospitalised patients (80, 177). Some of these patients probably have a non-Hp-associated ulcer and need peptic ulcer prophylaxis. However, for a substantial number of CRF patients reinvestigation should be undertaken according to guidelines before starting further treatment (212). Moreover, Hurenkamp and co-workers have recently shown that successful Hp eradication and ulcer healing in peptic ulcer patients makes further acid-suppressive therapy unnecessary (98). In Paper I we found that CRF patients consuming PPIs had higher GSRS scores for abdominal pain, indigestion and eating dysfunction. A possible explanation for the high prevalence of GI symptoms in these patients might be functional complaints, which are not acid-related and therefore exist in these patients despite PPI therapy.

Another common indication in many studies, including ours, was "no reason found", reflecting the obscure prescription and insufficient follow-up of acid-suppressive medication.

The majority of patients in Paper II had been treated with acid-suppressive drugs for a long period of time and long-term treatment has also been observed by others (80, 154, 177). There are some possible explanations for this. First, several physicians are often involved in the treatment of the patient and no one assumes responsibility for evaluating the efficacy of the acid-suppressive therapy. Secondly, rebound acid hypersecretion after

discontinuation of acid-suppressive therapy might result in reintroduction of the drugs. The rebound phenomenon has been well-established for both H_2-RAs and PPIs (72, 196). Recently, Smith and co-workers found that acid hypersecretion after discontinuation of ranitidine (H_2-RA) in healthy volunteers resulted in dyspeptic symptoms (196). In addition, uraemic patients have hypergastrinaemia related to the renal insufficiency (119). One can speculate about an additional effect of this hypergastrinaemia on rebound acid hypersecretion, leading to aggravated dyspeptic symptoms in CRF patients. Thirdly, long-term acid suppression with PPIs rarely produces adverse events (122) and PPIs are safe in the treatment of CRF patients (108, 118).

Whether the proportion of patients undergoing endoscopy in our study is sufficient or not is questionable. In a study from Australia, 67% of the patients had an endoscopy prior to or within one week of starting acid-suppressive therapy (154). In a recent study from our group the proportion of endoscopy before therapy varied a lot, ranging from 32% to 58% (157). It has been proposed that younger patients could be treated with acid-suppressive therapy for a short period without prior endoscopy (46). In case of relapsing symptoms after withdrawal of therapy, gastroscopy should be performed. The findings in other studies, in combination with the old age of the CRF patients and the high proportion of long-term treatment, point to a need for more frequent use of endoscopy in these patients.

Proton pump inhibitors were the dominating acid-suppressive drug in the present study, used by more than 90% of the patients. Similar results were recently found in another study from our group (157) and Naunton and co-workers also find a dominance of PPIs in hospitalised patients (154). However, in studies conducted in the US and other parts of Europe, a higher proportion of H_2-RAs was used (80, 83, 153, 162). It is conceivable that these differences might depend on varying prescription traditions in different countries and/or that H_2-RAs were more frequently used in the earliest studies.

To conclude, there is an overuse of acid-suppressive therapy in CRF as well as in many other diseases and conditions. Improved clinical practice in the management of acid-suppressive therapy will certainly lead to significant and substantial benefits in health care costs.

VISCERAL MOTILITY

The CRF patients in the gastric emptying study, particularly men, demonstrated a significant delay in emptying assessed by indigestible solids compared with healthy controls, which is in line with the majority of previous studies on gastric emptying in CRF (27, 45, 54, 106, 183, 226, 228). A variety of methods have been used in these studies, including radiologic methods, scintigraphy, breath tests and ultrasound, measuring both digestible and indigestible solids as well as liquids, which reinforces the statement that gastroparesis is a common finding among uraemic patients. Only a few studies have failed to show a slower emptying rate in uraemic patients (197, 214).

In contrast to previous gastric emptying studies in uraemic patients we compared women and men separately. The reason for this was to achieve better discrimination since gender differences in gastric emptying of liquids and digestible and non-digestible solids have been reported in healthy subjects, with a slower emptying rate in women (81, 179, 204, 219). Using this separate comparison, a substantial delay in gastric emptying in men with CRF was disclosed.

While gastric emptying is unaffected by age in men, some studies imply that elderly postmenopausal women have a more rapid emptying of digestible solids compared with younger fertile women (81). The older age in women with CRF in the present study compared with healthy women may therefore explain why there was no difference in the gastric emptying rate between these two groups. However, despite this age difference a significant proportion of female CRF patients, 24%, demonstrated delayed gastric emptying outside the reference range for healthy women. In summary, our findings imply that uraemic patients are at high risk of developing slow gastric emptying irrespective of gender.

The radiologic method using ROMs to assess gastric emptying has, to our knowledge, only been performed once before in CRF patients demonstrating a delay of gastric emptying (27). However, this method has been validated extensively (38, 165, 179, 204) and a good correlation to scintigraphy has been shown (165, 204). Furthermore, in contrast to scintigraphy, ROMs emptying is a simple, cheap and commonly available method and useful in clinical practice.

The manometry study is, to our knowledge, the first study on small bowel motility in patients with chronic renal failure. Recently, a French group has performed a study in dogs with moderate renal failure, demonstrating abnormal electrical activity of the small intestine in concordance with our results (124).

However, while the propagation velocity of the activity front (phase III) was increased in uraemic patients, it was decreased in the dogs. A plausible explanation for this discrepancy is that renal failure on a chronic basis induces changes other than the more experimental renal failure achieved in dogs. Whatever the case, the results from these two studies indicate that renal insufficiency has an impact on small bowel motility.

In agreement with several other manometry studies in different diseases and conditions, we observed a higher number of long clusters in CRF patients compared with healthy controls (20, 84, 112, 195, 201). One of the previous studies demonstrated a correlation between clusters and GI symptoms in IBS patients (112). However, in the majority of studies, no specific relationship between an assessed parameter and long clusters could be detected. It has been proposed that cluster activity might be a non-specific response to stress (168).

Another evident motor abnormality observed in uraemic patients was the higher frequency of retrograde pressure waves in the proximal duodenum, both in phase II and post-prandially compared with healthy controls. An increased prevalence of retrograde pressure waves has also been observed in patients with severe chronic dyspepsia (20), irritable bowel syndrome (195), and in patients with liver cirrhosis and portal hypertension (84). The clinical significance of the increased duodenal retroperistaltic motor pattern in patients with CRF as well as in the other patients is unclear. Previous studies in humans have demonstrated a relationship between small intestinal motility and the flow of contents in the fasting state (phases II and III) and post-prandially (116). The consequence of the retroperistaltic pressure waves might be a reduced flow of contents in the aboral direction. However, this motility pattern had no influence on GI symptoms, since there was no difference in the retroperistaltic activity between CRF patients with and without symptoms in the present study. It is conceivable that increased retrograde activity is a marker of GI dysmotility in these patients.

The uraemic state might have an influence on the degree of motor abnormalities, with more pronounced disturbances in CRF patients with severe uraemia. However, we were not able to support this hypothesis since there was no difference in serum urea levels between the different sub-groups of CRF.

There were both age and gender differences between the CRF patients and the healthy controls. However, it has been demonstrated that small intestine motility patterns are largely unchanged with age (101) and are independent of gender (19).

The pathophysiology of the alterations in the motility of the upper GI tract in uraemic patients is unclear and probably multifactorial. There are several conceivable mechanisms. Autonomic dysfunction has been demonstrated in CRF patients with delayed gastric emptying (54) and one possible explanation for the disturbed GI motility in CRF is that uraemic toxins have an effect on the autonomic and enteric nervous systems. Moreover, a great number of GI peptides are regulators of post-prandial motility and the increased levels of these GI hormones due to impaired renal clearance (161), might also play an important role in the mechanisms behind the disturbed GI motility in CRF.

Manometry offers the opportunity to evaluate the enteric neuromuscular function (100) and the method allows a simple estimation of the function of the enteric nervous system in CRF. This has, to our knowledge, never been done before.

The observed changes in both small intestinal motility and gastric emptying in our study might imply that these disturbances are related and recently a relationship between gastroparesis and small bowel dysmotility was reported (60).

BACTERIAL INFECTIONS IN THE GI TRACT

The high prevalence of small intestinal bacterial overgrowth (SIBO) demonstrated in the present study is in agreement with some previous studies (55, 190, 191). However, SIBO data are somewhat contradictory in CRF, with no increased prevalence of SIBO demonstrated in one study (58). As stated above, disturbed small intestinal motility might be a contributing factor for SIBO (99, 102, 202, 229). This may also be valid in CRF, since the uraemic patients with SIBO in our study showed a tendency towards a higher frequency of neuropathic-like motility pattern compared with the uraemic patients without SIBO. The lower proportion of antral phase III observed in CRF patients compared with the controls might also predispose to SIBO, and the absence of phase III activity in antrum and the small bowel has previously been related to SIBO (102, 202, 229).

Only one of the eight CRF patients with SIBO in the manometry study was treated with acid-suppressive therapy. As discussed above, acid-suppressive therapy contributes to both gastric and enteric colonisation with mostly gram-positive bacteria, but also with colonic bacteria (68, 180). However, the clinical significance of gram-positive bacteria in the small intestine is questionable (68,

180). Furthermore, in the definition of SIBO the growth of colonic bacteria (gram-negatives and anaerobes) is often added as a criteria (99).

In a recent study from our group (84) comparable findings with disturbed small intestinal motility and a high prevalence of SIBO were demonstrated in patients with liver cirrhosis and portal hypertension. These results may indicate a toxic effect on the enteric nervous system due to impaired renal and liver function respectively.

The prevalence of Hp infection in CRF patients reported in the literature, has shown somewhat contradictory results. However, the majority of these studies have found a similar or lower prevalence compared with the healthy population. In agreement with this, we demonstrated similar or lower prevalence of HP infection in CRF patients compared with previous studies. The serological tests are considered to have a lower sensitivity (62, 175). The prevalence of Hp infection in the present study might therefore be underestimated. Helicobacter pylori infection did not have any influence on gastric emptying, which is in agreement with results reported previously (106).

GASTROINTESTINAL SYMPTOMS AND PATHOPHYSIOLOGY

In the first paper of the thesis, we found that GI symptoms were common in patients with CRF. The second paper demonstrated a frequent use of acid-suppressive therapy, which probably reflects in part the high prevalence of GI symptoms in these patients. In the motility studies (III, IV), abnormal small intestinal motility and delayed gastric emptying and bacterial overgrowth in the small bowel were observed. However, the majority of findings were not correlated to GI symptoms in the uraemic patients. In other studies of gastrointestinal motility, both in CRF and other chronic diseases, it has been difficult to correlate symptoms with abnormal motility findings (106, 142, 143, 197). However, in the manometry study we observed a significantly higher propagation velocity of phase III in the duodenum in the symptomatic CRF patients compared with healthy controls and asymptomatic patients. This is interesting since diarrhoea was the dominating GI symptom. A shorter small bowel transit has been demonstrated in diarrhoea-predominant IBS patients (34, 78, 105). Moreover, a recent study in IBS patients has shown a correlation between retroperistaltic motility in the small bowel and diarrhoea (195). It is therefore tempting to hypothesise that the correlation between the increased

velocity of phase III and diarrhoea in CRF patients might be mediated through accelerated small bowel transit.

As discussed above, some authors have described a relationship between a delay in gastric emptying and GI symptoms. Patients in peritoneal dialysis in Paper I had more reflux symptoms and delayed gastric emptying was more common among PD patients in Paper IV compared with predialytic patients. Furthermore, the most common indication for acid-suppressive therapy in Paper II was GORD. These findings together indicate that GORD is common in PD patients and a contributing pathophysiological mechanism might be delayed gastric emptying. Van Vlem and co-workers have demonstrated delayed gastric in the presence of a glucose-based dialysate in the abdomen of PD patients (227) and they concluded that the delay in gastric emptying was more likely to be due to glucose absorption than to intraperitoneal volume load. Moreover, acute hyperglycaemia has been found to influence gastric emptying in diabetics (97) and small intestinal motility in healthy subjects (21). Furthermore, in a recent study from Turkey peritoneal dialysis treatment was related to GORD (35).

Bacterial overgrowth in the small intestine did not differ between the symptomatic and asymptomatic uraemic patients. Previous data on this is lacking.

The difficulty demonstrating an association between GI symptoms and abnormal findings may have some plausible explanations. Firstly, the number of patients in the studies might have been too low to demonstrate differences in abnormal findings between symptomatic and asymptomatic patients. Secondly, the abnormalities might be related to chronic renal failure *prse* and not to the presence of GI symptoms. Abnormal motility findings in CRF thus might be regarded as a marker for disturbed functioning of the enteric nervous system.

Further studies are needed to evaluate the pathophysiology behind GI symptoms in CRF.

SUMMARY AND CONCLUSIONS

1. CRF patients have a high prevalence of gastrointestinal symptoms. This finding might contribute to malnutrition, regarded as a marker of morbidity and mortality in renal insufficiency.

2. Gastrointestinal symptoms in CRF patients are associated with impaired psychological well-being, indicating the role of GI symptoms as an important factor affecting health-related QOL in end-stage renal disease.

3. Patients with CRF on dialysis have a high consumption of acid-suppressive drugs and long-term treatment is very common. Proton pump inhibitors are the dominating drugs.

4. The majority of the uraemic patients have an inappropriate use of acid-suppressive therapy, with dyspepsia and abdominal pain as the most frequent inadequate indications. The reasons for this overuse are probably multifactorial.

5. Manometry recordings of the small bowel in CRF patients demonstrated abnormal motility patterns compared with healthy controls, both in the fasting state and after a meal. Symptomatic CRF patients, all with diarrhoea, had increased propagation velocity of phase III in the duodenum. This finding may indicate a pathophysiological mechanism behind diarrhoea in CRF patients.

6. Small intestinal bacterial overgrowth was a common finding in CRF, irrespective of GI symptoms. Neuropathic-like motor patterns and disturbed phase III activity in CRF patients with SIBO indicate motility disturbances as a pathogenetic factor of SIBO in chronic renal failure.

7. Delayed gastric emptying is common in patients with CRF, particularly in men. This does not seem to be correlated with GI symptoms. However, a delay in gastric emptying was more frequent in PD patients. In combination with the higher prevalence of reflux symptoms found in PD patients, this

finding might reflect a relationship between delayed gastric emptying and GORD in patients on peritoneal dialysis.

8. The prevalence of Helicobacter pylori infection was low and had no impact on gastric emptying in CRF.

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