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Patients with chronic kidney disease have abnormal upper gastro-intestinal tract digestive function: A study of uremic enteropathy

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Abstract

Background and Aim: Chronic kidney disease (CKD) affects gastrointestinal (GI) function and results in numerous adaptive and maladaptive responses. Disruption of the colonic microbiome and its attendant consequences—the loss of gut barrier integrity and increased generation of uremic toxins—has become well-recognized. However, less attention has been paid to characterizing the mechanisms behind dysfunction of the upper GI tract, largely owing to the difficulty of studying small bowel function *in vivo*. This present study was designed to comprehensively describe upper GI function in those with advanced renal impairment.

Methods: Thirty-five non-diabetic subjects (12 CKD stage 4/5 patients, 23 healthy controls) underwent detailed GI magnetic resonance imaging (MRI) in both fasted and fed states. Upper GI function was assessed by quantification of gastric emptying and intraluminal small bowel water. Characterization of hydration and cardiovascular status was performed at baseline. Gut barrier integrity was assessed using serum endotoxin level.

Results: Chronic kidney disease was associated with dysmotility (gastric half-emptying time 96 ± 32 *vs* 74 ± 27 min, $P = 0.04$) and reduced fasting and post-prandial small bowel water (36 ± 22 mL *vs* 78 ± 42 mL, $P < 0.001$), reflecting abnormal digestive secretion, and absorption. This was related to the degree of endotoxemia ($r = -0.60$, $P = 0.04$) and poorer symptom scores, but not to disease severity, arterial stiffness or hydration status.

Conclusion: Chronic kidney disease adversely affects digestive function. Abnormalities in digestive secretion and absorption may potentially have a broad impact in the prevention and treatment of both CKD and its complications. Further study is required to assess the factors that contribute to this dysfunction in a wider CKD population.

Introduction

The complex relationship between the gastrointestinal (GI) tract and complications of chronic kidney disease (CKD) has been increasingly recognized over the past few years. Disruption to the colonic microbiome in CKD leads to an increase in the generation of uremic toxins and their subsequent systemic effects. Furthermore, it is now understood that this colonic dysbiosis also plays an important part in the development of a dysfunctional gut barrier and increased translocation of intestinal-derived factors, such as bacterial fragments, into the systemic circulation, driving inflammation, and cardiovascular disease.[1,2]

Chronic kidney disease is also characterized by adaptive changes to absorptive function in the remainder of the GI tract. These include various modifications to mineral absorption and excretion, altered drug elimination, and increased urate excretion.[3–5] In addition, a variety of less well-understood maladaptive responses have been identified. Animal models of chronic uremia have shown that the dysfunction observed with the defensive colonic barrier is mirrored in both the gastric and ileal mucosa, despite being relatively sterile,[6] although bacterial colonization is a feature of advancing CKD.[7] Studies have consistently demonstrated abnormal upper GI motility in those with renal impairment, which appears to worsen with advancing CKD stage.[8–10] Drug absorption and elimination have been shown to be abnormal within the small bowel, which has been proposed to be linked to accumulation of inflammatory cytokines, uremic toxins, and the effects of excess parathyroid hormone.[11,12] Abnormal small bowel digestive secretion has also been documented in several studies.[13,14] Combined, these abnormalities represent a dysfunctional phenotype, specific to CKD, which affects a significant proportion of the GI tract, beyond colonic dysbiosis. However, the pathophysiology underlying such findings, and the relative contribution of each proposed pathophysiological mechanism, particularly within the small bowel, remains poorly understood. Furthermore, the link between such changes and the commonly encountered GI symptoms experienced by those with renal impairment remains unclear; as does the association with malnutrition, a critical prognostic marker in advanced CKD.

The study of small bowel function in humans *in vivo* has previously been limited by the invasive and disruptive nature of required investigations. However, the development of functional GI imaging techniques now allows simultaneous, non-invasive assessment of GI structure and motility, as well as elements of digestive function through sequential study after feeding. In particular, assessment of small bowel water content (SBWC) provides an overall representation of digestive transit, secretion, and absorption for the entirety of the small bowel. This has provided valuable insight into both the physiology of digestion[15,16] and the pathophysiology of functional bowel disease, including enhancing explanation of symptom experience.[17,18] This pilot study was designed to use such techniques to comprehensively describe functional abnormalities of the upper GI tract in advanced CKD.

Materials and methods

Ethical considerations. The study was approved by the Derby Research Ethics Committee and conducted according to the standards of the Declaration of Helsinki, the International Conference on Harmonization and Good Clinical Practice Guidelines. All patients gave their written, informed consent to participate in the study.

Subjects. Twelve patients with advanced renal impairment (four with CKD Stage 4 and eight with CKD Stage 5) were recruited to a cross-sectional study from the prevalent CKD population treated at the Royal Derby Hospital, Derby, UK from May 2012–May 2013. All patients recruited with CKD Stage 5 were receiving treatment with peritoneal dialysis (duration 5–27 months).

Notable exclusion criteria included any known chronic GI disease (including Irritable Bowel Syndrome), a history of major GI surgery, prescription of drugs affecting GI motility, significant cardiovascular morbidity or diabetes.

Twenty-three healthy volunteers with normal renal function were recruited from the general population and were subject to the study imaging protocol as patient participants. Nine individuals underwent full assessment to include non-imaging procedures as per the patient group.

Study procedures

Magnetic resonance imaging assessment. Participants attended having fasted overnight, withheld caffeine, and alcohol for 24 h. Those patients receiving peritoneal dialysis were scanned without dialysate *in situ*. MR scanning was performed on a 1.5 T Phillips Achieva scanner, with specific imaging sequences performed for assessment of gastric motility and SBWC. After baseline scans, participants consumed a 331 kcal test meal of rice pudding, raspberry jam, and orange juice, followed by serial abdominal scans every 45 min for 4 h in order to assess GI response to the physiological stress of feeding.

Gastric emptying was assessed with a balanced gradient echo sequence to acquire 20 transverse images each with an in-plane resolution of 1.56 mm × 1.56 mm and slice thickness of 10 mm, with no gap between slices. Measurements of the gastric volumes were carried out by manually tracing regions of interest around the meal with the use of Analyze9 software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN) and summing across the slices. The time for half-emptying was calculated from the plots of volume against time.

Intra-luminal SBWC, representing net water absorption and secretion, was assessed using a validated method with a single shot, fast spin-echo sequence to acquire in a single breath-hold, 24 coronal images with in-plane resolution interpolated to 0.78 mm × 0.78 mm and a slice thickness of 7 mm, with no gap between slices (acquired voxel size $1.56 \times 2.83 \times 7\ mm^3$). These images were analyzed by a single trained operator with the use of in-house software. This methodology has been previously validated against intubation studies, using cerebrospinal fluid (CSF) as a threshold value (Fig. 1).[15]

Symptom assessment. The presence and severity of GI symptoms were assessed using the Gastro-intestinal Symptoms Rating Scale (GSRS), with overall symptom and psychological burden assessed using the SF-36 questionnaire and the Hospital Anxiety and Depression Score (HADS).

Other procedures. Non-invasive measurement of fluid status and hemodynamic function and blood collection were performed immediately prior to MR imaging. Systemic hemodynamic function was assessed non-invasively using a Finometer (TNO

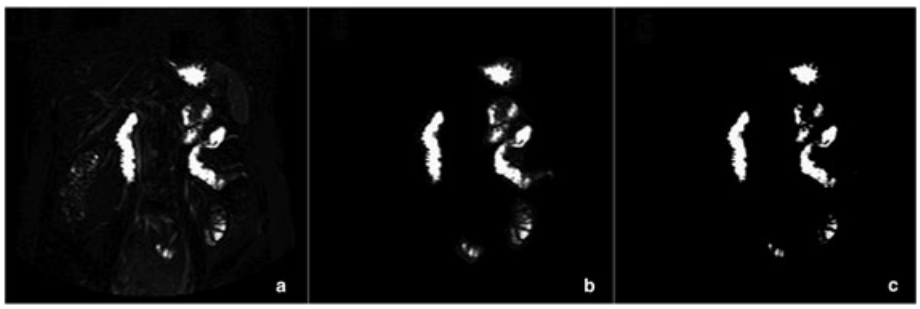

Figure 1 MR Assessment of Free-intraluminal Small Bowel Water: Illustration of the segmentation process. (a) Typical MRCP coronal image showing all tissues. (b) Segmented small bowel and stomach data having removed all data from blood vessels but background tissues surrounding bowel loops remain. (c) Data with signal greater than CSF reference value.

Instruments Amsterdam, Netherlands) which uses digital pulse wave analysis to record beat-to-beat hemodynamics. Data were collected for a 10 min period and then averaged. Pulse-wave velocity, a marker of arterial stiffness, was measured using dual cuff measurement with a Vicorder device (Skidmore Medical Ltd, Bristol, UK). Tissue bound advanced glycation end-products (AGE), a measure of cumulative metabolic stress, were measured non-invasively through the use of skin ultraviolet autofluorescence (AGE Reader; DiagnOptics, Groningen, The Netherlands). Body composition including extracellular water (ECW) was measured with multi-frequency, bioimpedance analyser (BIA: In Body® S20, Korea).

Serum lipopolysaccharide quantification was performed using a Limulus Amebocyte assay (Cambrex, Verviers, Belgium) using a previously described method.[19] Standard measures of renal and hematological function were also determined. For those healthy subjects who did not undergo blood sampling, endotoxin level was assumed to be undetectable on the basis of previous consensus that in health endotoxin does not circulate systemically.[20]

Statistical analysis. Statistical analysis was performed using SPSS version 22 (IBM, Chicago, IL). Parametric data are expressed as mean ± SD and non-parametric data as median (interquartile range). All continuous variables were tested for normality using the Shapiro-Wilk test. Parametric continuous data were compared between the two groups using the independent *t* test and non-parametric data using the Mann Whitney *U* test. The association between categorical variables was tested using the Chi-squared test. Correlation between two variables was determined using Pearson's coefficient. Where data were only available for the smaller subgroup of healthy volunteers, analysis was censored accordingly. An alpha error of 0.05 or less was judged to be significant.

Results

Group characteristics. Demographic characteristics of both groups are shown in Table 1. The CKD group were significantly older than the healthy subjects and had a higher BMI. However, the groups were balanced in terms of gender, smoking status, and alcohol intake.

The CKD group demonstrated biochemical and cardiovascular characteristics typical of that expected in advanced renal impairment. Calcium and phosphate were elevated with albumin levels significantly lower in the patient group, despite having a higher average BMI. The patient group exhibited evidence of increased arterial stiffness with higher pulse-wave velocity (9.13 ± 1.6 m/s *vs* 7.03 ± 1.3 m/s, $P = 0.008$). However, assessment of fluid status demonstrated no objective evidence of significant overhydration (ECW 16.0 ± 3.3 L *vs* 16.3 ± 2.6 L, $P = 0.84$) and blood pressure was relatively well controlled (mean arterial pressure (MAP) 97.1 ± 17.0 *vs* 92.3 ± 13.2 mmHg, $P = 0.73$). Endotoxemia was universal in CKD patients and absent in healthy subjects (0.19 ± 0.04EU/mL *vs* < 0.10EU/mL, $P < 0.001$).

Gastro-intestinal assessment. Gastric emptying was significantly prolonged in the CKD group with the half-emptying time 96 ± 32 min compared with 74 ± 27 min in healthy participants ($P = 0.04$) (Fig. 2). Four CKD patients had gastric half-emptying times above 107 min, which has been shown to be the upper limit of normal for a healthy population.[21] Two patients had more than 30% of their meal still present in the stomach 180 min after ingestion.

Both CKD patients and healthy subjects demonstrated a high degree of variability in all measurements of SBWC, with fasting SBWC ranging from 10–104 mL in patients and 9–226 mL in healthy subjects. However, fasting SBWC tended to be lower in CKD patients (53 ± 48 mL *vs* 83 ± 63 mL, $P = 0.16$). Healthy volunteers exhibited a normal post-prandial response[17] with SBWC initially falling sharply after ingestion of food then gradually rising from 45 min to a plateau approximately 135 min after the meal. However, CKD patients exhibited a sustained fall

Table 1 CKD and healthy participant population characteristics

	CKD patients ($n = 12$)	Healthy controls ($n = 23$)	*P* value
Age (yrs)	69.5 ± 10.3	30.0 ± 14.3	<0.001
Gender (M/F)	7/5	14/9	0.75
BMI (kg/m^2)	27.8 ± 3.65	22.7 ± 3.17	0.004
Smoking status (Non/ex/curr)	(7/3/1)	(22/1/0)	0.39
Alcohol intake (units/week)	2 (0–6)	8 (0–18)	0.25
SBP (mmHg)	145 ± 28	125 ± 13	0.36
DBP (mmHg)	75.8 ± 14.2	72.9 ± 11.3	0.79
Hemoglobin (g/dL)†	12.1 ± 1.5	14.6 ± 1.3	0.002
Calcium (mmol/L)†	2.51 ± 0.1	2.41 ± 0.0	0.01
Phosphate (mmol/L)†	1.05 ± 0.3	0.79 ± 0.2	0.02
Albumin (g/dL)†	33.0 ± 5.2	39.7 ± 3.6	0.008

†Data available for nine volunteers only Parametric data are expressed as mean ± SD and non-parametric data as median (interquartile range). BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

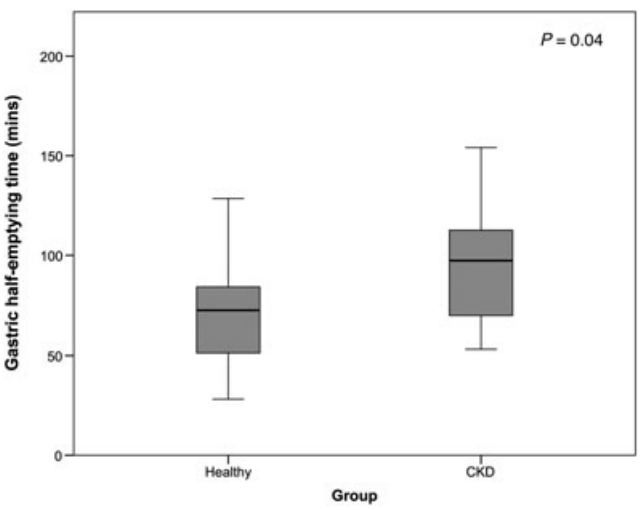

Figure 2 Comparison of Gastric-emptying in chronic kidney disease patients compared with healthy subjects after a test meal.

in SBWC with values falling until 90 min, with a delayed rise back to pre-prandial levels (Fig. 3). SBWC was significantly lower in the CKD group at 90, 135, and 180 min but not at 225 min (Table 2). Cumulative SBWC was significantly lower in CKD patients (275 ± 168 *vs* 440 ± 223 mL, $P = 0.03$). Reduced post-prandial SBWC was associated with a higher level of endotoxin ($r = -0.60$, $P = 0.04$) (Fig. 4) but not with age, creatinine, symptom scores, arterial stiffness or markers of hypervolemia (ECW, systolic blood pressure).

Symptom scores. Chronic kidney disease patients had significantly higher symptom burden compared with the subgroup of healthy subjects, reflected in GSRS assessment, depression, and physical health scores (Table 3). A higher gastro-intestinal symptom score was associated with worse depression, physical, and mental health scores ($r = 0.74$, $P = 0.002$; $r = -0.94$, $P < 0.001$; $r = -0.79$, $P = 0.002$, respectively). A delay in gastric-emptying was also associated with a higher GSRS score ($r = 0.56$, $P = 0.04$ for gastric volume 135 min after the test meal). However, fasting and post-prandial SBWC were not significantly associated with GSRS, anxiety, depression or physical healthy symptom scores.

Discussion

This study is the first to examine dynamic small bowel function in CKD patients. We have shown using detailed MR based imaging that non-diabetic patients with advanced renal impairment exhibit upper GI dysfunction, including abnormal handling of small bowel water. This relates to symptoms, overall quality-of-life, and increased gut permeability with higher systemic exposure to circulating endotoxin.

Intraluminal small bowel water reflects the balance between transit of GI contents, intestinal absorption, and secretion. In healthy subjects, total SBWC reduces acutely after ingestion due to rapid colonic transit of terminal ileal contents with rapid

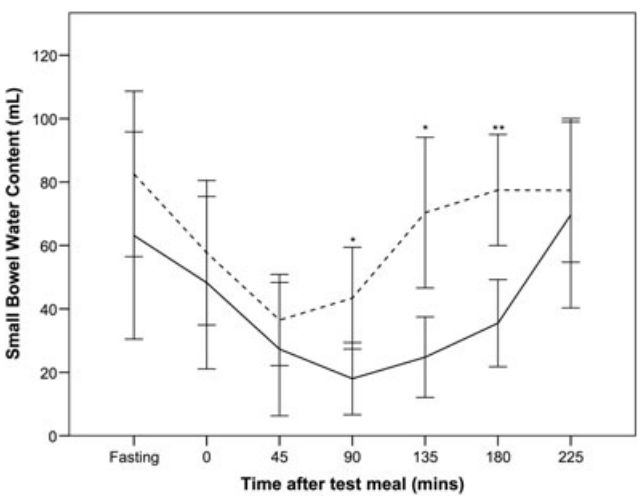

Figure 3 Fasting and post-prandial intraluminal small bowel water content in chronic kidney disease patients compared with healthy subjects. Error bars represent 95% confidence interval. * = significant $P < 0.05$, ** = significant $P < 0.001$.

Table 2 Summary of major fasting and post-prandial findings in CKD patients and healthy subjects

	CKD patients ($n = 12$)	Healthy controls ($n = 23$)	*P* value
Fasted SBWC (mL)	53 ± 48	83 ± 63	0.16
SBWC 90 min (mL)	17 ± 17	43 ± 39	0.03
SBWC 180 min (mL)	36 ± 22	78 ± 42	<0.001
SBWC 225 min (mL)	70 ± 46	77 ± 55	0.67
Gastric half emptying time (min)	96 ± 32	74 ± 27	0.04
ECW (L)[†]	16.6 ± 3.0	16.3 ± 2.6	0.84
Endotoxin (EU/mL)	0.19 ± 0.04	All <0.1	<0.001

[†]Data only available for nine healthy subjects. Parametric data are expressed as mean ± SD and non-parametric data as median (interquartile range).
CKD, chronic kidney disease; ECW, extracellular water; SBWC, small bowel water content.

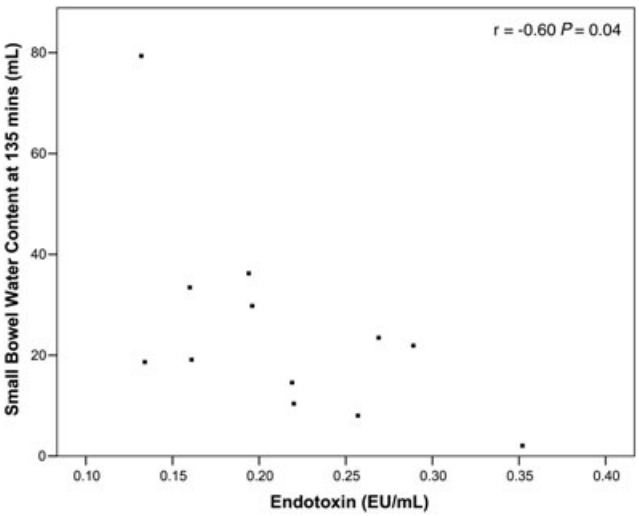

Figure 4 The relationship between post-prandial small bowel water content and endotoxemia in chronic kidney disease patients.

Table 3 Comparison of general and gastrointestinal specific symptom scoring between CKD patients and a subgroup of healthy subjects

	CKD patients ($n = 12$)	Healthy controls ($n = 9$)	*P* value
HADS Anxiety	4 (1–7)	3 (1–4)	0.48
HADS Depression	4 (2–6)	0 (0–3)	0.01
SF36 Physical health score	37 (23–43)	52 (47–58)	0.002
SF36 Mental health score	53 (49–63)	59 (49–61)	0.83
GSRS Score	6 (2–18)	1 (0–2)	0.005

Data are expressed as median (interquartile range).
CKD, chronic kidney disease; GSRS, gastro-intestinal symptoms rating scale; HADS, hospital anxiety and depression score.

absorption of glucose, fructose, and sucrose from an ingested meal. There is then a slow rise in intra-luminal bowel water as gastric contents move into the jejunum and digestive secretion occurs, coupled with the gradual absorption of water from the ileum. The sustained decrease and delayed rise in SBWC in CKD patients could be partially explained by delayed gastric emptying as less volume transits into the small bowel as is absorbed or passes into the colon. However, this alone is not sufficient to explain the difference in fasting SBWC values or in those from 180 to 225 min, where gastric emptying contributes minimally to alterations in small bowel water volume. At these times, digestive secretion and water absorption are the major factors determining SBWC, suggesting that there is abnormal digestive function in the small bowel in CKD patients.

Renal impairment is well known to disrupt intestinal homeostasis in the large bowel through alteration in the composition of gut microflora, direct influence of uremia on the enterocyte, and the intra-luminal production of uremic toxins.[22] However, small intestinal digestive dysfunction in patients with kidney disease has not previously been identified. The impact of abnormal small bowel handling of digestive contents is potentially broad and relates to both small intestine and colonic function. Within the small bowel, water secretion, and absorption plays a critical role in the digestion of food. The intra-luminal osmotic gradient is a key determinant of digested nutrient absorption in the highly permeable jejunum. Furthermore, water acts as an active co-transporter for both glucose and sodium within the proximal small intestine, regardless of osmotic gradient.[23]

Perhaps more relevant to CKD is the influence that small bowel function, and water absorption in particular, has upon colonic function. The amount of sodium and water absorption within the large bowel is determined by the composition of ileal effluent, thereby affecting stool composition and also potentially affecting overall body volume status. In a similar study of patients with Diarrhoea-Predominant Irritable Bowel Syndrome, a delayed post-prandial rise in SBWC was observed and strongly associated with increased transit time and severity of diarrhoeal symptoms.[17]

The rate of delivery and composition of small bowel effluent to the large bowel also considerably alters the balance of the colonic microbial population[24] potentially therefore affecting bowel wall permeability and uremic toxin generation. In these subjects, endotoxin levels were related to SBWC, implying a link between this observed digestive dysfunction and the increased gut barrier permeability. However, it should be noted that endotoxin itself has been shown to directly affect bowel motility and water flux with increased transit times reported in sepsis in humans and after direct inoculation in animal studies in a dose-dependent manner.[25,26] This may be a causal factor rather than merely a consequence of small bowel dysfunction.

Determining the key contributing mechanisms behind this observed abnormal upper GI function in CKD is clearly important, however, the small size and cross-sectional nature of this study unfortunately limits the scope for assessment of such factors. Indeed, the surprisingly large variability in measured SBWC in both groups implies that there are many different factors that determine small bowel water. In assessment of potential confounders, it is important to note that the patient group were significantly older than the group of healthy controls. However, gastric motility and SBWC have been shown to be unaffected by increasing age in several previous studies.[17,27,28] In CKD, others have suggested accumulation of circulating inflammatory cytokines, uremic toxins, bacterial overgrowth, and uremia to be key determinants of dysfunction in the GI tract. Here, the degree of uremia and renal impairment did not appear to be associated with the degree of dysfunction and we were unable to assess the composition of small bowel microbiota. However, endotoxin—a potent pro-inflammatory stimulus—was associated with reduced SBWC.

The small size of the study group also meant that we were unable to meaningfully examine specific characteristics in those receiving renal replacement therapy in subgroup analysis. However, future studies utilizing advancing imaging methodology need to be designed to further elucidate the pathophysiology that underpins functional enteropathy in renal impairment. This will include broadening the populations studied, to include other modalities of renal replacement therapy and earlier stage CKD.

Conclusion

In conclusion, this pilot study demonstrates that small bowel digestive function is markedly abnormal in a population of CKD patients and is symptomatically important. In order to fully understand and potentially treat the GI consequences of CKD, future attention ought to be directed towards the factors that influence this digestive dysfunction as well its impact upon other recognized consequences of advanced renal impairment.

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