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Randomized Control Trials

An iso-osmolar oral supplement increases natriuresis and does not increase stomal output in patients with an ileostomy: A randomised, double-blinded, active comparator, crossover intervention study

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SUMMARY

Background: Patients with an ileostomy often experience fluid and electrolyte depletion because of gastrointestinal loss. This study aimed to compare how an iso-osmolar and a hyperosmolar oral supplement affect ileostomy output, urine production, and natriuresis as proxy measurements of water-electrolyte balance.

Methods: In a randomised, double-blinded, active comparator, crossover intervention study, we included eight adult ileostomy patients who were independent of parenteral support. We investigated how an iso-osmolar (279 mOsm/kg) and a hyperosmolar (681 mOsm/kg) oral supplement affected ileostomy output mass, urine volume, and natriuresis. In addition to their habitual diet, each participant ingested 800 mL/day of either the iso-osmolar or hyperosmolar supplement in each of two study periods. Each period started with 24-hour baseline measurements, and the supplements were ingested during the following 48 h. All measurements were repeated in the last 24 h.

Results: No statistically significant changes in ileostomy output were detected following the intake of either oral supplement (median (range) 67 (−728 to 290) g/day, $p = 0.25$) despite increased fluid intake. Compared with the hyperosmolar supplement, the iso-osmolar supplement induced a statistically significant increase in urine volume (470 (0–780) mL/day, $p = 0.02$) and natriuresis (36 (0–66) mmol/day, $p = 0.02$).

Conclusion: Intake of the two oral supplements did not affect ileostomy output during this short intervention. Natriuresis increased following intake of the iso-osmolar supplement compared to that after ingesting the hyperosmolar supplement, indicating that patients with an ileostomy may benefit from increasing their ingestion of iso-osmolar fluids. *ClinicalTrials.gov identifier:* NCT03348709.

1. Introduction

An ileostomy is formed during surgery following resection of the colon or parts of the small bowel. Bowel resections reduce the intestinal surface area and may lower the capacity for the absorption of nutrients, fluid, and electrolytes [1]. Normally, most gastrointestinal secretions are reabsorbed, but following a colectomy, both absorption of ingested foods and fluids and reabsorption of endogenous fluid may be decreased [2], with high stomal output as a consequence. Therefore, dehydration and electrolyte abnormalities are frequent in patients with an ileostomy [3,4]. These

Abbreviations: ECV, extracellular volume; IBD, inflammatory bowel disease; ICV, intracellular volume; IF, intestinal failure; HPN, home parenteral nutrition; ORS, oral rehydration solution; Pt, patient.

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patients have high gastrointestinal sodium losses and tend to be sodium-depleted despite having normal plasma values [5,6]. Some patients develop a dependency on intravenous fluid and nutritional support, a condition referred to as intestinal failure (IF) [7]. Home parenteral nutrition (HPN) is a life-saving therapy that normalises fluid balance and increases quality of life, but its inherent risks of complications, including catheter-related blood stream infections and venous thromboembolism, should be considered [8,9]. Methods to orally optimise the energy, fluid, and electrolyte balances of ileostomy patients are warranted.

Osmolality is a measure of millimoles of solutes per kg of solvent [10], and the osmolalities of fluids present in the proximal intestines may affect the absorption of nutrients, water, and electrolytes [11]. Because water transport across epithelial membranes follows solutes in response to a local osmotic gradient [12], intraluminal hyperosmolality feasibly induces extracellular volume (ECV) flux into the lumen if nutrient absorption capacity is saturated. Normally, duodenal osmoregulation suppresses the release of non-iso-osmolar gastric contents [13]. A colectomy may, however, result in accelerated gastric emptying [14]. If the duodenal osmoregulation is overwhelmed because of the rapid release of gastric content, the influence of intraluminal osmolality could be particularly important for absorption in ileostomates. Following colectomy, the intake of hyperosmolar solutions may hypothetically increase the intestinal losses of nutrients, fluids and electrolytes. Furthermore, fluids without sufficient sodium content can cause water and sodium flux from plasma into the intestinal lumen [2,15,16]. Taken together, this phenomenon would leave few suitable oral fluid choices for ileostomates, e.g., oral rehydration solutions (ORS), broth, and milk. Avoiding both hyperosmolar solutions, such as conventional oral nutritional supplements, lemonade, fruit juices, soft drinks and alcoholic beverages, as well as hypo-osmolar fluids, such as water, tea, and coffee, may be burdensome. This may partially explain why dehydration and sodium depletion remain clinical challenges in this patient group.

In the present study, we investigated how the osmolalities of liquid oral supplements affected stomal output, natriuresis, and urine volume in patients with an ileostomy to explore ways to orally optimise their fluid and electrolyte balance.

2. Materials and methods

2.1. Study design and participants

This was a single-centre, randomised, double-blinded, active comparator, crossover intervention study. The effects of osmolality in oral supplements were investigated using a 2 × 2 crossover design. The oral supplements were administered during two separate three-day intervention periods, with a washout period of at least 14 days separating the two periods. Only mentally capable adults were included. Eight consecutive eligible patients in contact with the outpatient clinic at Aarhus University Hospital in Denmark who consented to participation were included (Fig. 1). The inclusion criteria were as follows: at least age of 18 years, had an ileostomy constructed at least six weeks before enrolment, able to ingest at least 1000 mL of fluids per day, and consent to participation. If the patient had inflammatory bowel disease (IBD), they were required to be in clinical remission, estimated by the *Physician Global Assessment*. The study exclusion criteria were as follows: weight gain/loss above 5 kg within the last three months prior to enrolment, intolerance to dairy products, known chronic kidney disease, known diabetes mellitus, or enteral tube feeding or parenteral nutrition/fluid more than twice a week.

The eight patients with an ileostomy were included in this study between April 2017 and October 2017. The causes for ileostomy formation were IBD (n = 7) and cancer (n = 1). Seven participants had no signs of active bowel inflammation. One participant with Crohn's disease (pt 5) was in clinical remission but had slightly increased faecal calprotectin (478 mg/kg). All patients were outpatients and managed with loperamide (n = 3), proton pump inhibitors (n = 4), and adalimumab (n = 1). Two participants (pt 4 and 6) regularly consumed oral rehydration solutions (ORS). None of the participants received any parenteral support, and they were not at nutritional risk, as assessed by the NRS-2002 screening tool [17].

2.2. Data collection

Each intervention period started and ended with clinical examinations, blood samples, and 24-hour measurements at the Department of Hepatology and Gastroenterology of Aarhus University Hospital in Denmark. The participants were required to fast for at least 3 h before data collection was initiated. Measurements acquired within the first 24 h in each study period, including the registrations of dietary intake, ileostomy output and urine volume, served as the baselines. Participants ingested the intervention supplements during the following 48 h. The 24-hour registrations of dietary intake, ileostomy output and urine volume were repeated during the last intervention day.

The participants were at home during the intervention periods. After receiving thorough instructions, they handled the intake of the intervention supplements, registration of their dietary intake and ileostomy output, and collection of urine themselves throughout the baseline days and the last 24 h in both study periods. The participants used sickness bags (1500 mL, Mediplast, Lynge, Denmark) and a kitchen scale (2 kg/1 g, Funktion, Viborg, Denmark) to weigh their output. They collected urine in urine containers (3000 mL, Sarstedt, Nümbrecht, Germany) and delivered it to the investigators along with their registrations of intake and mass of ileostomy output either after the baseline day or after completion of the intervention period. The participants delivered the collected urine within 24 h or refrigerated it until delivery. Urine volume (mL) was determined by the same investigator each time using an integrated scale on the container. Blood samples and samples of mixed urine were analysed for sodium content and osmolality immediately after delivery.

2.3. Oral supplements and dietary intake

Two oral supplements were developed for this study. The iso-osmolar (276 mOsm/kg) and hyperosmolar (681 mOsm/kg) oral supplements were identical except for their contents of sucralose and glucose. Sucralose (0.001%, 0.03 mmol/L) was added to the iso-osmolar supplement to minimise taste differences, and the difference in osmolality was established by adding glucose (6.25%, 347 mmol/L) to the other oral supplement. Both supplements contained water, hydrolysed whey protein (4.5%), cocoa powder (3.42%), and sucrose (1.45%, 42 mmol/L). The energy and water contents of the two supplements differed because of the difference in glucose concentrations. The iso-osmolar supplement contained 142 kJ/100 g and 91% water, while the hyperosmolar supplement contained 238 kJ/100 g and 84% water.

The oral supplements were refrigerated (≈5 °C) until ingestion. The participants were instructed to drink 200 mL of the supplements four times a day for two days and to not eat or drink anything else an hour before and after ingestion of the oral supplements. The participants were instructed to maintain their habitual dietary intake except for substituting 800 mL of their daily fluid intake with the intervention supplement on the second and third days of the intervention periods. They were instructed to reduce their intake of milk or water with 800 mL/day, when substituting their habitual

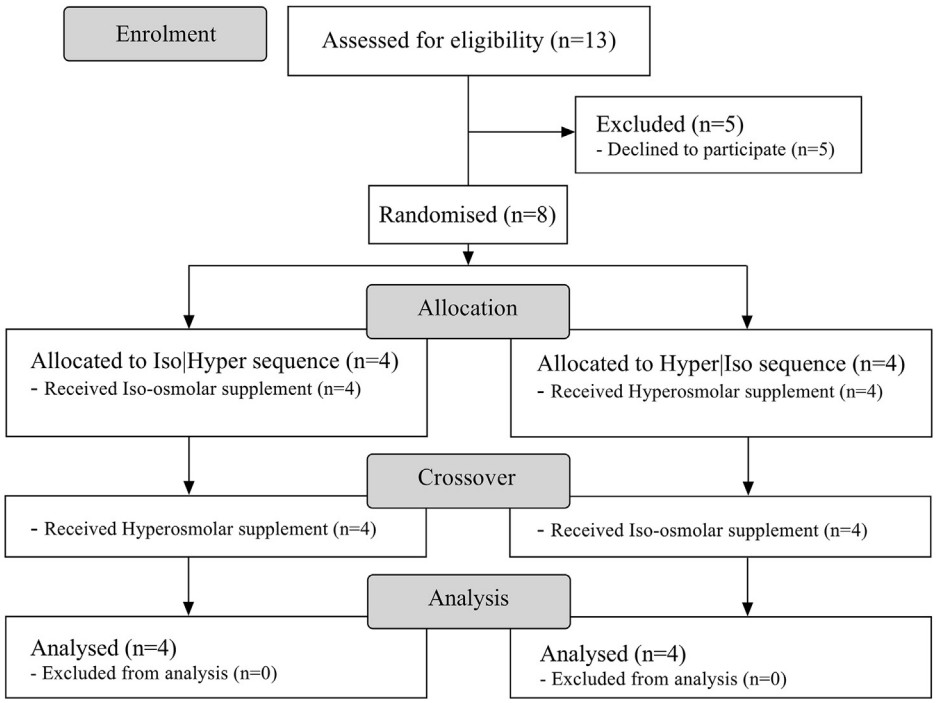

Fig. 1. Flow chart. Out of 13 ileostomates assessed for eligibility, eight patients consented to participation. The participants were randomised to receive either the iso-osmolar supplement before the hyperosmolar supplement (Iso|Hyper) or vice versa (Hyper|Iso). All participants (n = 8) completed both intervention periods and were included in the analyses.

beverages. The participants kept dietary records in both intervention periods and registered all food and fluid intake in household measures, by weighing their intake or by taking pictures, according to their own preferences. The first day in the first study period served as a proxy for their habitual intake, and the participants were asked to carefully duplicate this food and fluid intake the remaining days in both study periods. This was implemented to minimise variations in ileostomy output, natriuresis, and urine volume due to altered intakes, without excessive changes in their usual intake by using standardised diets. A registered dietitian calculated the participants dietary intake with the online software Madlog Vita (Madlog ApS © 2006–2018, Kolding, Denmark).

2.4. Randomisation and blinding

The participants were randomised to receive either the iso-osmolar oral supplement in their first intervention period (Iso-|Hyper) or the hyperosmolar supplement (Hyper|Iso). A 1:1 balanced randomisation key was computer-generated by the Clinical Trial Unit at Aarhus University. One of the primary investigators (CR) enrolled the participants, and they were assigned to interventions in the order they were recruited. Both the investigators and the participants were blinded to the allocation. Two unblinded study nurses prepared two identical boxes with the two different oral supplements for each participant corresponding to the randomisation key. The boxes did not contain any information regarding their content.

2.5. Outcome measures

Primary outcome: difference in ileostomy output (g/day, wet weight) between the baseline and last treatment day following ingestion of the iso-osmolar and hyperosmolar oral supplement. *Secondary outcomes:* urine volume (mL/day), urine sodium (mmol/day), urine osmolality (mmol/kg), plasma sodium (mmol/L), plasma osmolality (mmol/kg), plasma creatinine (μmol/L) and estimated intakes of fluids (all beverages) (mL/day), total water (combined water content from beverages and foods) (%), energy (kJ/day), total food and fluid intake (g/day), and sodium (mmol/day).

2.6. Statistical considerations

The sample size was calculated prior to the crossover investigation using an estimated *within patient* standard deviation of 140 mL of ileostomy output/day, a minimum relevant difference between the intervention treatments of 300 mL of ileostomy output/day, a type I error of 0.05 and a type II error of 0.20 (power = 0.80). This calculation indicated that a sample size of n = 6 patients was required for a crossover design. We added 25% to allow for dropouts, resulting in a sample size of n = 8 patients to investigate.

Non-parametric statistical intention-to-treat analyses were performed with GraphPad Prism 7.0 (GraphPad Software, San Diego, USA). A two-tailed Wilcoxon matched-pairs signed rank test was used for the analyses of differences in dietary intake, blood samples, ileostomy output, urine volume and natriuresis. Treatment effects were assessed with the paired differences (Δ-Δ-values) between the treatment and baseline measurements in each intervention period. Differences between the first and second baselines were calculated to assess their comparability before and after the washout period. Blinding of the participants was assessed with a two-tailed binomial test. The results are presented as percentages or median (range) values, and p-values < 0.05 were considered statistically significant.

2.7. Ethical statement

All patients provided informed and written consent to participate. Overall, the study was conducted in accordance with the Declaration of Helsinki. The experimental protocol was approved

by the Central Denmark Regional Committee on Health Research Ethics (j.no. 1-10-72-12-17) and the Danish Data Protection Agency (j.no. 1-16-02-627-16) prior to the investigation. The study protocol was registered at www.clinicaltrials.gov (identifier: NCT03348709).

3. Results

3.1. Baseline measurements

Eight adult patients with an ileostomy were included. Patient characteristics, crossover sequence, and length of washout periods are presented in Table 1. The participants' median (range) age was 64 (25–76) years, and their median BMI was 26.5 (21–38) kg/m^2. The median time since ileostomy formation was 11.5 (6–49) years. Three participants (pt 1, 7 and 8) had increased plasma creatinine (98–119 μmol/L). Plasma osmolality was above 300 mmol/kg for two participants (pt 3 and 7) at enrolment, and the median was 299 (289–305) mmol/kg. There were no statistically significant changes post-interventions. Urine osmolality in fasting morning spot urine samples was above 900 mmol/kg for two participants (pt 3 and 6), and the median was 768 (413–1156) mmol/kg. No significant differences were observed following either intervention.

There were no statistically significant differences between the baselines in the two study periods. The fluid intakes at the baseline measurements of each study period were comparable, i.e., 2025 (1250–3150) mL/day at the first baseline and 1875 (1230–3150) mL/day at the second baseline ($p = 0.06$). The median (range) ileostomy output mass at the first baseline was 1083 (439–2007) g/day compared with 1223 (493–1643) g/day at the second baseline ($p = 0.74$). The median (range) natriuresis values were 51 (20–93) mmol/day at the first baseline and 37 (18–82) mmol/day at the second baseline ($p = 0.16$). The median (range) urine volumes were 1065 (580–1680) mL/day at the first baseline and 975 (500–2010) mL/day at the second baseline ($p = 0.68$). The lower limit of urinary sodium detection was approximately 20 mmol/L, and participants with a natriuresis of less than 20 mmol/day may therefore have had undetectably low sodium concentrations in their urine samples.

3.2. Effectiveness of blinding

The participants were requested to guess which supplement they received in the last study period. Six participants thought they could distinguish the two supplements, and three (50%) answered correctly ($p > 0.99$).

3.3. Primary and secondary outcomes

3.3.1. Dietary intake

Fluid intake (all beverages) increased significantly from the baseline to the last treatment day in both periods despite advising the patients to replace and not add the intervention supplement to their habitual fluid intake. The participants reduced their normal beverage intake with ≈500 mL/day, while ingesting 800 mL/day of the intervention supplements. Following the iso-osmolar supplement, fluid intake increased 355 (−50 to 950) mL/day from the baseline to the last treatment day ($p = 0.02$). After the hyperosmolar supplement, fluid intake increased 315 (−150 to 850) mL/day ($p = 0.03$) (Fig. 2A). There was no statistically significant difference between the treatments, with a median difference of −15 (−600 to 350) mL/day ($p = 0.56$) (Fig. 2B).

The percentages of total water intake from both beverages and water from foods were comparable between the intervention periods. Hypo-osmolar fluids (water, coffee, tea, and mineral water) comprised a median (range) of 48% (4–65) of the total water intake during the iso-osmolar intervention period and a median 48% (8–66) during the hyperosmolar intervention period. In addition to

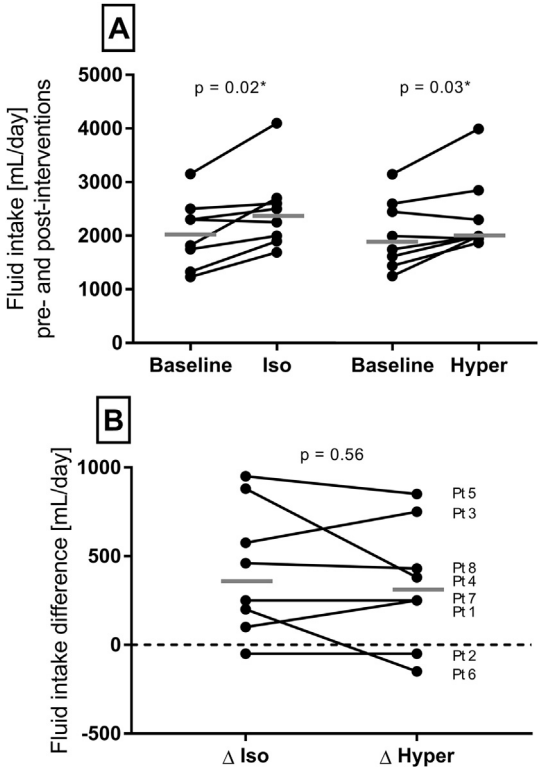

Fig. 2. The fluid intake increased during both intervention periods. Data obtained from dietary records (n = 8), presented as trendlines and medians (grey lines). A: Twenty-four-hour fluid intake pre- and post-intervention periods. B: Difference in fluid intake between pre- and post-intervention, following each supplement (Δ-values). Iso, iso-osmolar oral supplement; Hyper, hyperosmolar oral supplement; Pt, patient.

Table 1
Baseline characteristics.

Pt	Age [years]	Sex	Weight [kg]	Height [cm]	BMI	Years with stoma	Primary disease	Estimated bowel length [cm]	Sequence	Washout [days]
1	66	m	85	180	26	44	UC	350	Iso|Hyper	20
2	52	f	98	175	32	13	UC	350	Iso|Hyper	49
3	71	f	67	157	27	37	UC	350	Hyper|Iso	16
4	62	f	97	160	38	10	CD	150	Iso|Hyper	39
5	25	m	87	172	29	6	CD	320	Hyper|Iso	17
6	47	m	74	172	25	6	UC	230	Hyper|Iso	17
7	73	f	69	176	22	9	Cancer	340	Iso|Hyper	16
8	76	f	50	153	21	49	UC	200	Hyper|Iso	24

The first eight consecutive eligible and consenting patients with an ileostomy were included in this crossover intervention study. If no measurements were noted following surgery, the length of remaining small bowel was estimated to be 350 cm, and three patients had no ileal resections. Pt, patient; UC, ulcerative colitis; CD, Crohn's disease; Iso, iso-osmolar oral supplement; Hyper, hyperosmolar oral supplement.

the intervention supplements, iso-osmolar beverages (milk and ORS) comprised 10% (0–50) of the total water intake during the iso-osmolar intervention period and 9% (0–38) during the hyperosmolar intervention period. Hyperosmolar beverages (conventional oral nutritional supplements, lemonade, fruit juices, soft drinks, and alcoholic beverages) comprised 7% (0–13) of the total water intake during the iso-osmolar intervention period and 5% (0–15) during the hyperosmolar intervention period. Water from foods comprised 18% (12–29) of the total water intake during the iso-osmolar intervention period and 21% (12–27) during the hyperosmolar intervention period. The median difference in sodium intake was −3 (−111 to 44) mmol/day (p = 0.95), and the median difference in energy intake (not including the oral supplements) between the interventions was −113 (−1847 to 3600) kJ/day (p = 0.25). There were no significant differences in total food and fluid intakes between the interventions (median −20 (−360 to 484) g/day, p = 0.74).

3.3.2. Stomal output

The ileostomy output did not change significantly following either intervention supplement. The median difference following the iso-osmolar supplement increased 66 (−307 to 490) g/day (p = 0.31). After hyperosmolar supplementation, the stomal output decreased 85 (−487 to 176) g/day (p = 0.31) (Fig. 3A). There was no statistically significant difference between treatments (67 (−728 to 290) g/day, p = 0.25) (Fig. 3B). Three participants had a post-intervention difference in stomal output of more than 300 g/day, while the other differences ranged from 17 to 237 g/day.

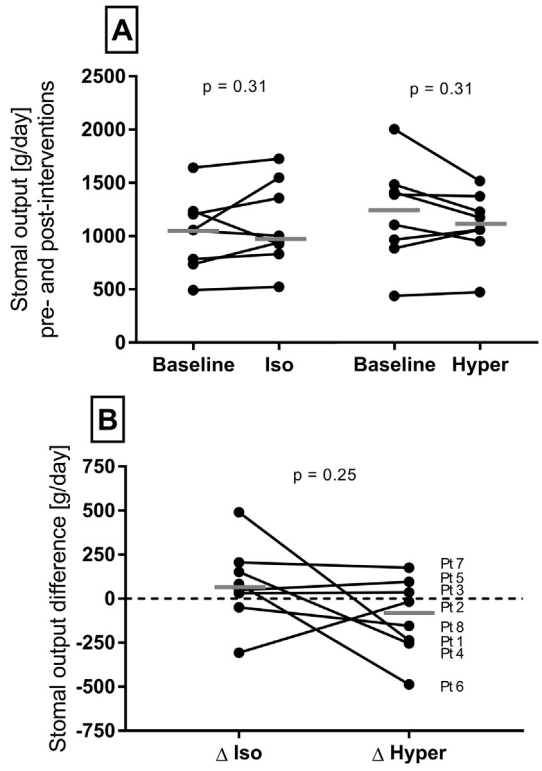

Fig. 3. The ileostomy output did not change significantly following intake of either oral supplement. Data obtained from weighing stomal output (n = 8), presented as trendlines and medians (grey lines). A: Mass of 24-hour ileostomy output pre- and post-intervention periods. B: Difference in ileostomy output between pre- and post-interventions, following each oral supplement (Δ-values). Iso, iso-osmolar oral supplement; Hyper, hyperosmolar oral supplement; Pt, patient.

3.3.3. Sodium and urine volume

All participants (n = 8) had normal plasma sodium values pre- and post-intervention periods (median (range) 140 (137–143) mmol/L), and there were no statistically significant differences between the baselines and treatments or between the baseline measurements.

Urine volumes were statistically significantly higher following intake of the iso-osmolar supplement (305 (0–840) mL/day, p = 0.02). Following the hyperosmolar treatment, urine volume decreased 35 (−350 to 360) mL/day (p = 0.81) (Fig. 4A). Most participants (n = 7) increased their urine volume in the iso-osmolar study period, while half of the participants (n = 4) had lower urine volumes following ingestion of the hyperosmolar supplement. The iso-osmolar supplement resulted in a 470 (0–780) mL/day higher urine volume than the hyperosmolar supplement (p = 0.02) (Fig. 4B). Natriuresis tended to increase following the iso-osmolar treatment (20 (−19 to 69) mmol/day, p = 0.08) and decrease after hyperosmolar treatment (−7 (−54 to 3) mmol/day, p = 0.09) (Fig. 4C). When comparing natriuresis levels between the two study periods, we observed a statistically significant increase in natriuresis following intake of the iso-osmolar supplement (36 (0–66) mmol/day, p = 0.02). Natriuresis increased in most participants (n = 6), decreased in one, and remained unchanged in one during the iso-osmolar treatment compared with the baseline. During the hyperosmolar treatment, natriuresis increased in one patient, decreased in six and remained unchanged in one compared with the baseline (Fig. 4D).

4. Discussion

In this short-term crossover study on ileostomy patients who were independent of parenteral support, we observed unchanged ileostomy outputs following the intake of liquid oral supplements regardless of osmolality and an increased overall fluid intake. Importantly, we observed statistically significantly higher natriuresis and urine volume following intake of the iso-osmolar supplement compared with those following ingestion of the hyperosmolar supplement. The short timeframe may have rendered some results inconclusive, yet it may be substantial and clinically relevant that such a small change of beverage osmolality clearly indicated an effect on water-electrolyte balances.

Previous studies indicated that hyperosmolar oral supplements increase stomal output. Andersson et al. found increased stomal outputs following the intake of a hyperosmolar liquid diet in patients with extensive small bowel resections (>100 cm) [18]. Rat models and triple-lumen tube perfusion studies on subjects with intact small bowels showed a negative correlation between osmolality and intestinal water absorption [11,19]. In this study, we could not adjust for bowel length, and the hyperosmolar oral supplement could have feasibly increased the stomal output in patients with the highest degree of malabsorption or during an intervention period longer than 48 h. Further, the osmolality of 681 mOsm/kg in the hyperosmolar supplement was lower than that of some hyperosmolar beverages, which have osmolalities well above 700 mOsm/kg [20,21]. The hydrolysed proteins used in both oral supplements may have reduced the effective osmolality. The effective osmolality of an oral supplement depends on the selectiveness of the mucosal permeability [10], which varies with segments of the small intestines [22]. If hydrolysed proteins or other nutrients are absorbed, they presumably instead facilitate improved fluid and electrolyte absorption. Moreover, hydrolysed proteins may elicit a different effect on gut hormones and gastrointestinal secretions than intact protein [23]. These phenomena could potentially explain why neither oral supplement generated

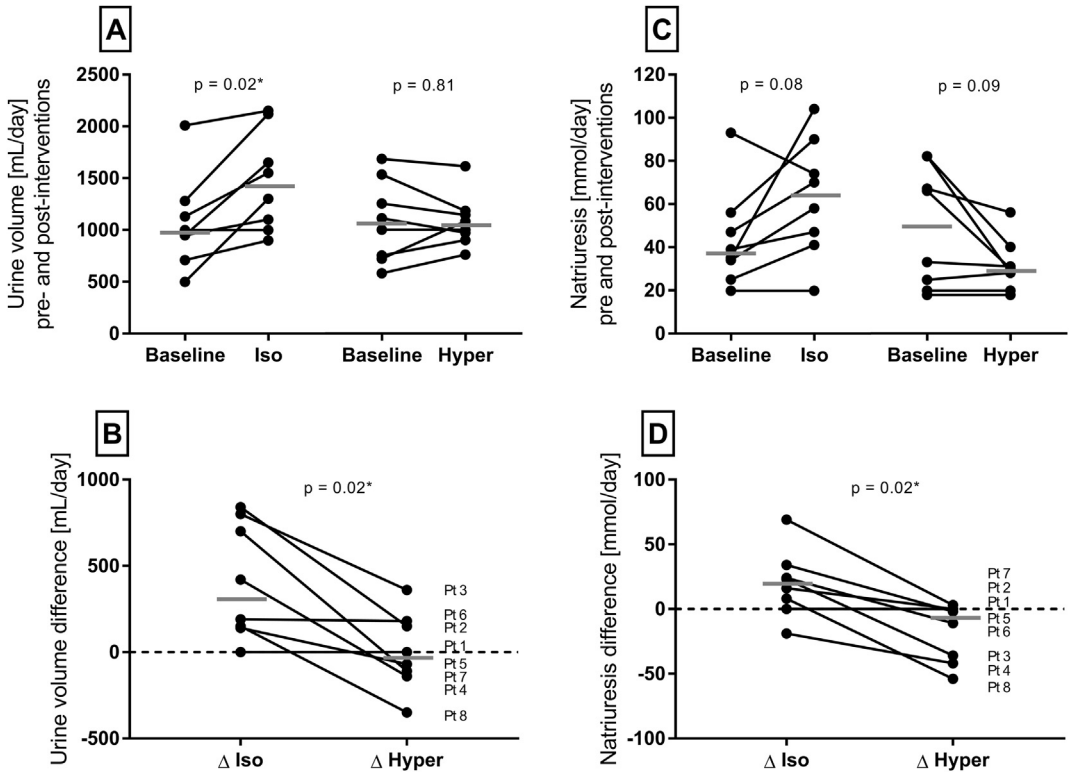

Fig. 4. The urine volume and natriuresis increased following intake of the iso-osmolar supplement. Data obtained from urine collections (n = 8), presented as trendlines and medians (grey lines). A: Volume of 24-hour urine output pre- and post-intervention periods. B: Difference in urine volumes between pre- and post-intervention, following each oral supplement (Δ-values). C: Renal sodium excretion (natriuresis) pre- and post-intervention periods. D: Difference in natriuresis levels between pre- and post-intervention, following each oral supplement (Δ-values). Iso, iso-osmolar oral supplement; Hyper, hyperosmolar oral supplement; Pt, patient.

an increased stomal output, even though the oral supplements were responsible for an overall increased fluid intake.

Our finding that intake of the iso-osmolar supplement increased urine volume and natriuresis compared with the hyperosmolar supplement indicates improved intestinal water and sodium absorption. This may represent an early reaction to the effect of different osmolalities in the ingested fluids. Water absorption is influenced by gastrointestinal secretions, local osmotic gradients, active absorption of solutes, sodium concentration, gastric emptying, and exercise [24]. The two supplements in this study differed by only low-dose sucralose in the iso-osmolar supplement (0.03 mmol/L) versus glucose in the hyperosmolar supplement (347 mmol/L). Glucose increases net water absorption [25] to a certain point at which the transport capacity is saturated [11]. The hyperosmolar supplement had a glucose concentration above the absorption capacity (≈250 mmol/L) [26], which may have led to net secretion of water. This, however, does not explain why neither stomal or urine output increased following the hyperosmolar supplement. We hypothesise that the sum of small, statistically insignificant differences in intakes and outputs were responsible for this discrepancy. Sodium absorption is affected by different factors, e.g., sodium concentration, intestinal segment, water movement, and the presence of glucose or amino acids [27]. The oral supplements used herein had low sodium contents (13.5 mmol/L), which could have theoretically resulted in sodium secretion into the lumen [15,16,27], but this contradicts the increased natriuresis we observed following the iso-osmolar supplement. Consistent with our results, Andersson et al. showed a significantly larger net sodium absorption in ileostomates receiving a 350 mOsm/kg osmolality diet compared with that in those receiving a diet of higher osmolality (440 mOsm/kg) [18]. The ratio between sodium and glucose is important as well, and a low ratio may induce intestinal sodium secretion [19], which could be contributing to the significantly increased natriuresis following the iso-osmolar supplement, compared to the hyperosmolar supplement.

A natriuresis level below 100 mmol/day is associated with decreased nutritional, mineral and bone statuses for ileostomates [3]. All participants in this study had a natriuresis level below 100 mmol/day at baseline, with half of the participants below 50 mmol/day despite normal plasma sodium concentrations. Numerous studies have documented that ileostomates have low natriuresis levels in combination with normal plasma values [3,5,6,28–31]. Turnberg et al. showed that seemingly healthy ileostomates may be intracellularly depleted of sodium and potassium [28]. Their results indicate that the regulation of ECV volume and osmolality is prioritised over intracellular sodium and potassium concentrations. Gastrointestinal losses may be compensated by the exchangeable reserve of sodium, i.e., the concentrations in the intracellular volume (ICV) and ECV, and the constant normalisation of ECV could explain the absence of clinical signs of dehydration and electrolyte disturbance. Ileostomates are normally recommended a sodium-rich ORS to minimise gastrointestinal sodium losses [1,2]. In this study, the intakes of ORS and sodium were stable, and the participants presumably had unchanged renal functions between the two intervention periods. The increased natriuresis that we observed, indicates that iso-osmolar beverages may potentially be suitable for ileostomates despite having low sodium concentrations. However unlikely, we cannot exclude that the difference in natriuresis was caused by an altered renal reabsorption of sodium. The circulating ECV normally determines the size of natriuresis, which is especially mediated by vasopressin, but it may also be affected by other hormones or factors [32]. Investigations of changes in hormone levels or the

expression of different transporters and channels could be informative but were not included in the present study.

Sucralose is generally regarded as an inert food additive, but some studies indicate that non-nutritive sweeteners may have metabolic effects, and perhaps affect intestinal motility, and glucose and sodium absorption [33]. This potentially affected our results by improving glucose and sodium absorption and thereby increasing net water absorption. However, the low concentration of sucralose (10 mg/L) in the iso-osmolar supplement may be negligible, and conventional beverages with sucralose have concentrations that are 4–10 times as high [34].

Our study has important limitations. Due to the short time frame, the patients did not reach a steady state. The hyperosmolar fluid used in this study is not necessarily comparable to regular hyperosmolar fluids, such as fruit juices and soft drinks. The different energy contents in the two supplements could have caused different gastric emptying rates [35] and different gastrointestinal secretions [36], thereby biasing our results. Food intake was calculated from dietary records instead of weighed intake registrations. Finally, we did not standardise physical activity during the study. Differences in physical activity could introduce differences in gastric emptying rates [24] and glucose absorption [11]. Because the patients were stable during the study period and the two interventions were comparable, we found this bias to be negligible.

In conclusion, we observed no statistically significant changes in stomal output following the intake of 800 mL/day of an iso-osmolar or hyperosmolar supplement within 48 h. Urine volume and natriuresis levels increased with intake of the iso-osmolar supplement compared with those following hyperosmolar supplementation. A study with a longer time frame is needed to investigate whether the intake of iso-osmolar oral supplements may reduce stomal output and help patients with an ileostomy reach a steady state with an improved water and electrolyte balance.

Statement of authorship

Conception and design of the study: C Rud, AKN Pedersen, TL Wilkens, M Borre, JR Andersen, CL Hvas. Acquisition of data: C Rud, AKN Pedersen, JF Dahlerup, CL Hvas. Analysis and interpretation of data: C Rud, ANK Pedersen, HB Moeller, CL Hvas. Drafting the article: C Rud, AKN Pedersen, CL Hvas. Critically revising the manuscript for important intellectual content: TL Wilkens, M Borre, HB Moeller, JF Dahlerup, JR Andersen. Final approval of the version to be submitted: all authors

Conflict of interest

C Rud declares non-financial support from University of Copenhagen, Denmark. AKN Pedersen declares non-financial support from University of Copenhagen and salaries from Aarhus University, Denmark. JF Dahlerup declares lecture fees unrelated to the present publication from Pharmacosmos, Takeda, MSD. CL Hvas declares lecture fees unrelated to the present publication from Takeda, Arla Foods Ingredients, MSD, Ferring. All other authors declare no conflicts of interest.

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