

Article

Not peer-reviewed version

---

# Bicarbonate Natural Mineral Water from Source “Aqua 3” Facilitates Digestion: A Preliminary Study

---

[Alessandro Zanasi](#)\*, [Fabio Pace](#), [Giorgio Zoli](#), [Aladin Abu Issa](#), [Antonio Maria Morselli-Labate](#)

Posted Date: 23 March 2026

doi: 10.20944/preprints202603.1812.v1

Keywords: carbonated water; digestion; drinking water; dyspepsia; gastroesophageal reflux; gastrointestinal diseases; mineral waters; PAGI-SYM questionnaire



Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a [Creative Commons CC BY 4.0 license](#), which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Article

# Bicarbonate Natural Mineral Water from Source "Aqua 3" Facilitates Digestion: A Preliminary Study

## Bicarbonate Mineral Water: Effect on Digestion

Alessandro Zanasi <sup>1,\*</sup>, Fabio Pace <sup>2</sup>, Giorgio Zoli <sup>3</sup>, Aladin Abu Issa <sup>2</sup>  
and Antonio Maria Morselli-Labate <sup>4</sup>

<sup>1</sup> Water Resource Association, Via Grotta 20, San Lazzaro di Savena, 40068 Bologna, Italy

<sup>2</sup> Gastrointestinal Unit, Bolognini Hospital, 24068 Seriate, Italy

<sup>3</sup> Internal Medicine, University of Ferrara, 44042 Ferrara, Italy

<sup>4</sup> Independent Consultant Biostatistician, 40043 Marzabotto – BO, Italy

\* Correspondence: zanasi.tosse@gmail.com

### Abstract

**Background:** The intake of mineral water for therapeutic purposes (crenotherapy) in digestive system disorders is a long-established practice, even though there are still few controlled clinical studies confirming the effect of natural mineral water rich in bicarbonate. **Objective:** To verify whether the daily intake of Aqua 3 bicarbonate natural mineral water is able to improve digestion in a population of patients with functional dyspepsia and gastroesophageal reflux disease symptoms. **Methods:** Patients had a diagnosis of functional dyspepsia formulated in accordance with the Rome IV criteria and were subjected to three periods of 2 weeks: tap water (wash-out), bicarbonate natural mineral water, and oligomineral water. The mineral water bottles had their labels removed. Primary efficacy endpoint: improvement in the PAGA-SYM total. Secondary endpoints: improvements in the PAGA-SYM subscales, in the use of antacids, and in the self-assessment of efficacy on digestion. **Results:** The PAGA-SYM total score and the six subscales significantly decreased after bicarbonate mineral water intake, while they significantly increased after oligomineral water supplementation. The antacid use was significantly different comparing the decrease after oligomineral water *versus* the increase after oligomineral water. In addition, the score of the subjective assessment of effectiveness of the patient's digestion was significantly better after the intake of bicarbonate than after oligomineral water. **Conclusions:** In line with the evidence reported in the literature, the findings of this study provide additional support for recommending natural bicarbonate mineral water as a symptomatic treatment for functional dyspepsia and gastroesophageal reflux disease. The intake of Aqua 3 bicarbonate mineral water proved to be a simple, safe, and natural intervention capable of improving digestive symptoms in patients with functional dyspepsia and reflux-related disorders, while promoting the digestive process.

**Keywords:** carbonated water; digestion; drinking water; dyspepsia; gastroesophageal reflux; gastrointestinal diseases; mineral waters; PAGA-SYM questionnaire

---

## 1. Introduction

### 1.1. Natural Mineral Waters

Since ancient times, man had understood that the waters flowing from particular sources could not only quench thirst, but possessed healing virtues. The first edict in the world on the exploitation of underground water resources and groundwater dates back to May 1605. It was signed by Henry IV of France, who pioneered the creation of "managers of mineral baths and fountains" in each

province of the kingdom, attributing to the First Court Doctor the function of choosing and coordinating the new “Ministers” of mineral waters [1].

Which kind of water can be defined as mineral? Natural mineral waters are those that, originating from an underground aquifer or deposit, come from one or more natural or drilled springs and have particular hygienic characteristics and properties that are favorable to health. Natural mineral waters are distinguished from ordinary drinking water for their original purity and conservation, for their mineral content and/or other constituents, and for their effects. Mineral waters represent a unique reality, distinct from all other types of water and for this reason they are regulated by specific European regulations [2,3].

The composition, temperature and other essential characteristics of natural mineral waters must remain constant at the source within the natural variations, even after any changes in flow rate. Compared to common tap water, mineral water must therefore possess specific characteristics: the difference lies in the fact that natural mineral waters are originally pure, must come from springs or underground aquifers, be microbiologically pure, have a characteristic and constant content in mineral salts and trace elements, boast a special recognition by the Ministry of Health and be bottled near the source. Furthermore, it cannot undergo any sanitizing treatment. Natural mineral water is considered to be that which is offered for use as it flows from the source: the purity at the source, in a chemical and bacteriological sense, is kept unaltered until consumption. Most mineral waters have meteoric origin and therefore follow the hydrogeological cycle, re-emerging to the surface after a variable underground path. During the underground journey, the waters mineralize, coming into contact with the rocks, and acquire peculiar, different and specific characteristics for each water. The different types of soil crossed also account for the different gaseous component, free or in solution. Carbon dioxide can, for example, have an atmospheric, calcareous or volcanic origin, while hydrogen sulfide can have a volcanic, organic or sulfur deposit origin. These processes occur in accordance with dissolution mechanisms (gases and salts) and chemical attack (hydration, protolysis, oxide reduction and ion exchange). Finally, in the subsoil, both by virtue of the geothermal gradient and the heating produced by volcanic phenomena or by mixing with gases or liquid layers of deep origin, the waters usually have a higher temperature than that detectable at the point of origin.

### 1.2. Classification of Natural Mineral Waters

The fixed residue is the best-known parameter, which allows a first distinction between mineral waters (Table 1). This quantitative classification, however, should not generate confusion: it only concerns the quantity of minerals contained in a liter of water and not the type. The legislation currently in force reports another classification of mineral waters, which is based on the presence of the predominant and qualifying chemical elements, on the basis of which it is possible to predict, at least theoretically, the biological, dietary and medicinal effects of a mineral water. Based on the types and quantity of mineral salts present, we can thus distinguish mineral waters according to the classification shown in Table 2.

**Table 1.** Classification of natural mineral waters based on fixed residue at 180 °C.

Fixed residue at 180 °C	Definition
≤50 mg/L	Very low mineral content water (or light mineral water)
50–500 mg/L	Low mineral content water
500–1,500 mg/L	Medium mineral content water
>1,500 mg/L	Rich mineral content water

**Table 2.** Classification by dominant ions.

Ion	Concentration
Bicarbonate (HCO <sub>3</sub> <sup>-</sup> )	>600 mg/L
Sulfate (SO <sub>4</sub> <sup>2-</sup> )	>200 mg/L
Chloride (Cl <sup>-</sup> )	>200 mg/L

<b>Calcium (Ca<sup>2+</sup>)</b>	>150 mg/L
<b>Magnesium (Mg<sup>2+</sup>)</b>	>50 mg/L
<b>Fluoride (F<sup>-</sup>)</b>	>1 mg/L
<b>Ferrous (Fe<sup>2+</sup>)</b>	>1 mg/L
<b>Sodium (Na<sup>+</sup>)</b>	>200 mg/L

---

### 1.3. Mineral Water and Digestion

A good hydration is essential to maintain the body water balance, although needs may vary among people. However, worldwide population is far from the recommended allowance for water intake [4–6]. Water is also considered a key element in promoting regular intestinal function. Drinking during meals promotes gastric digestion and emptying and results, at the liver level, in an increase in the flow of bile and bile acids, facilitating digestion and in particular the assimilation of fatty acids. In contact with water, then, the fibers tend to swell and, by pressing on the walls of the intestine, stimulate contractions and promote the speed of transit by softening the walls of the colon, eliminating constipation and preventing diverticula. Thus, the so-called “mineral waters”, thanks to their particular chemical composition, seem to actively intervene on different phases of the digestive process.

The study of the possible therapeutic role of mineral water constitutes a real science, called “medical hydrology” (or “thermal medicine”), a medical discipline that studies: i) the structural characteristics of the means of thermal care; ii) the manner of their application; iii) their biological and pharmacological actions; iv) their therapeutic effects. The digestive tract is one of the most investigated areas in the hydrological field and, although the data currently available suggest that crenotherapy with mineral water can constitute a useful complement to the medical treatment of functional digestive symptoms, solid scientific evidence on the mechanisms underlying the favorable effects of these waters on gastrointestinal functions are lacking [7,8].

The mechanism of action of mineral waters must be sought in the ability to act on different moments of the digestive act: gastric digestion, fractional emptying of the stomach, introduction of acidic chyme into the duodenum, stimulus to the release of gastrointestinal hormones, hepato-bilio-pancreatic secretory intervention, hydrolysis food and absorption, bilio-duodenal contractile correlation, transport movements at the colon level and evacuation. The different biological effects of mineral waters are linked to the different quantitative and qualitative presence of dissolved minerals, this explains why mineral waters carry out different actions, depending on their physical and chemical composition. We have long known the influences of Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Mg<sup>2+</sup> on variations in the membrane potential of myocytes. Ca<sup>2+</sup> ions, stimulate the secretion of gastrin,<sup>9</sup> functionally collaborate with second messengers (intracellular cyclic nucleotides), stimulate the secretion of gastric and duodenal HCO<sub>3</sub><sup>-</sup>, [10] stimulate pancreatic exocrine secretion, [11] some of such activities are antagonized by Mg<sup>2+</sup>, which in turn favors the opening of the sphincter of Oddi for probable stimulus to the release of CCK; the release of CCK is stimulated by SO<sub>4</sub><sup>2-</sup> anions, active in addition on the secretion of H<sub>2</sub>O and HCO<sub>3</sub><sup>-</sup> from the enterocytes of the intestinal lumen via activation of intracellular AMPc; the HCO<sub>3</sub><sup>-</sup> anion exerts buffering action on gastric acid secretion. We therefore understand the researchers’ effort aimed at identifying the influences of mineral waters on exocrine and endocrine digestive secretions, motility and, to a lesser extent, endoluminal digestion and absorption of nutrients. In particular, the waters rich in bicarbonates are those that have been shown to promote digestion, mitigate gastric hyperacidity, improve intestinal transit and help in resolving functional disorders such as the dyspeptic ones [12–19]. Specifically, it has been found that mineral waters characterized by a high concentration of bicarbonate and calcium ions are able to modulate the secretion of peptide hormones at the level of the gastrointestinal system [13,20] with secretion of endogenous gastrin and by the activation of the serotonin system [21]. It is known how the control of gastric secretion is operated through nervous pathways and humoral factors; among the latter, a prominent role is played by gastrin [22]. Knowledge of changes in plasma gastrin after intake of

mineral waters can therefore be a key to interpreting the mechanisms of action of these waters on some functions of the digestive tract [13,16,23,24].

#### 1.4. Functional Gastrointestinal Disorders and Impaired Digestion

Functional gastrointestinal disorders affect approximately one-third of the population and are one of the most common reasons for medical consultations, accounting for over 50% of gastroenterology consultations [25,26]. These disorders are characterized by persistent and recurrent gastrointestinal (GI) symptoms and occur as a result of abnormal functioning of the GI tract. They are characterized by a combination of chronic or recurrent symptoms, in the absence of obvious anatomical or biochemical alterations, and significantly impact the quality of life of those affected. These symptoms can manifest in different parts of the digestive tract and include abdominal pain, bloating, diarrhea, constipation, nausea, and vomiting. Dyspepsia (from the Greek “dys,” meaning difficult, and “pepsis,” meaning digestion) is a common symptom in the general population suggestive of gastroduodenal disorders. When occurring in the absence of a recognizable underlying disease, dyspepsia is defined functional dyspepsia (FD). According to the Rome IV criteria FD is an umbrella term referring to a patient who fulfills diagnostic criteria for postprandial distress syndrome (PDS) and/or epigastric pain syndrome (EPS). PDS refers to patients complaining of bothersome postprandial fullness and/or early satiation, while EPS patients complain of bothersome epigastric pain or burning. The term bothersome implies that symptoms need to be severe enough to somewhat impact on usual activities. PDS and EPS can co-exist in the same patient. Epigastric bloating, heartburn, excessive belching, nausea and or vomiting and digestive symptoms modified by bowel movements can also be present but are not dyspeptic symptoms. Criteria must be fulfilled in the last 3 months before diagnosis [27]. Conventional pharmacological treatment in these patients is often ineffective or only partially effective. Numerous scientific studies demonstrate that mineral water, particularly those rich in bicarbonates and calcium, can help improve symptoms associated with functional dyspepsia by modulating the motor and secretory activity of the gastrointestinal tract. These studies suggest that these waters may be beneficial for the treatment of functional digestive tract disorders. The main digestive tract conditions that benefit from crenotherapy are functional dyspepsia and digestive disorders related to gastroesophageal reflux disease (GERD) [12,28,29].

#### 1.5. Aim of the Study

This preliminary study was aimed at verifying whether the intake of  $\geq 1.5$  L/day of bicarbonate mineral water for 2 weeks is able to positively influence GERD symptoms and to promote digestive activity in subjects affected by FD and GERD symptoms.

## 2. Materials and Methods

### 2.1. Study Design

In order to prevent inclusion of patients with dyspeptic symptoms secondary to insufficient water intake a wash-out period with a minimum intake of 1,500 mL of tap water was required before entering the study. After inclusion each patient received 24 liters (1,500 mL/day supplementation for 16 days) of a bicarbonate water (Aqua 3, Carpathian Springs S.A., Vatra Dornei, Romania) in unmarked bottles. At the end of this two-week period, patients had to return remaining bottles (if any) in order to receive the second test supply of a similar quantity of unmarked bottles of a commercially available oligomineral water (Table 3).

**Table 3.** Main chemical-physical characteristics of tap water from the Bergamo aqueduct (Wash-out), bicarbonate mineral water (Aqua 3) and oligomineral water (Maintenance).

	Bergamo aqueduct tap water (Wash-out)	Bicarbonate mineral water (Aqua 3)	Oligomineral water (Maintenance)
Fixed residual at 180 °C	218.0 mg/L	672.1 mg/L	132.9 mg/L
pH at source	8.0 UpH	6.1 UpH	7.8 UpH
Free CO <sub>2</sub> at source	N/a	821.1 mg/L	3.5 mg/L
Bicarbonates (HCO <sub>3</sub> <sup>-</sup> )	222.0 mg/L	781.1 mg/L	134.0 mg/L
Sulfates	20.0 mg/L	7.8 mg/L	1.8 mg/L
Potassium	0.80 mg/L	3.89 mg/L	0.73 mg/L
Sodium	6.5mg/L	73.0 mg/L	3.9 mg/L
Calcium	50.0mg/L	158.1 mg/L	35.2 mg/L
Magnesium	14.0 mg/L	34.4 mg/L	5.3 mg/L
Fluorides	0.06 mg/L	0.06 mg/L	0.05 mg/L
Chlorides	3.0 mg/L	6.7 mg/L	1.3 mg/L
Silica	N/a	N/a	16.4 mg/L
Nitrates (NO <sub>3</sub> <sup>-</sup> )	5.0 mg/L	<0.06 mg/L	3.9 mg/L
Nitrogens	N/a	<0.02 mg/L	N/a

N/a: Not available.

Both bicarbonate and oligomineral water intake involved drinking 250 mL in the morning upon waking, and the remaining amount spread during the meals and over the course of the day.

A validated symptom questionnaire (PAGI-SYM) [30–32] was administered in the presence of a physician at entry (T0, baseline), at the end of the wash-out period (T1), and at the end of the first (T2, after bicarbonate mineral water) and of the second (T3, after oligomineral water) two-week study period. The wash-out period was chosen in order to avoid the possible bias due to effect of the increased hydration. On the other hand, the first two-week study period after wash-out (T2) allowed us to collect data on the effectiveness of the intake of bicarbonate mineral water, while the second two-week study period (T3) was chosen in order to evaluate if the effect of bicarbonate mineral water may be maintained after its suspension. Since there are no data available in the literature on the effect of mineral water on PAGI-SYM questionnaire, we made this preliminary study in order to collect the data needed for scheduling a final randomized cross-over controlled trial for comparing bicarbonate mineral *versus* oligomineral water. Due to the reason that this study represents a non-controlled study, we intentionally avoid to apply the cross-over experimental design.

Finally, all patients were asked to maintain their usual eating and lifestyle habits for the entire duration of the study, as well as, their daily intake of mineral water was limited to the delivered study supply. Nutritional supplements, probiotics and digestive therapies in general were not allowed; only on demand antacids were allowed and their intake was monitored during the study.

## 2.2. Inclusion Criteria

Participants meeting the following criteria were included: patients affected by FD, as defined by the Rome IV criteria for FD; [27] aged 18 years or older; they had not taken antibiotic, probiotic, prebiotic, and symbiotic medications for at least 2 weeks before enrollment, as well as, any pump inhibitors.

The participants agreed to participate in this study and signed an informed consent form.

## 2.3. Exclusion Criteria

The exclusion criteria were: patients with comorbid organic, metabolic, systemic or mental disorders; previous major surgeries; participation in other clinical trials within the past 6 months; patients with reverse osmosis or other water purification systems at home.

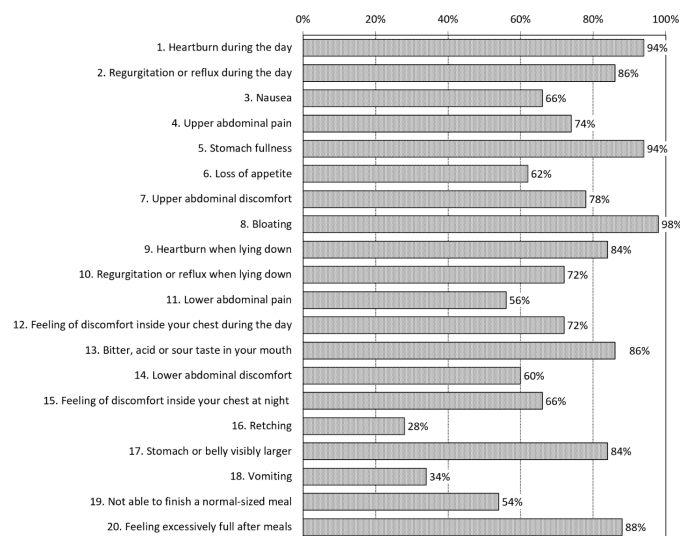
## 2.4. Patients

Fifty FD patients were enrolled. The diagnosis of FD was formulated in accordance with the Rome IV criteria on the basis of the symptoms and the absence of organic alterations documentable on physical examination and excluded by upper GI endoscopy [27].

All patients were Caucasian and baseline demographic and clinical characteristics are shown in Table 4. Most patients had normal weight (23, 46.0%), or were overweight (22, 44.0%), while only 4 (8.0%) were obese. Only one patient was underweight (2.0%). The 20-item symptoms of the PAGI-SYM questionnaire at baseline are shown in Figure 1. All patients had PDS (bothersome postprandial fullness and/or early satiety), as well as all of them had EPS (bothersome epigastric pain or burning).

**Table 4.** Baseline clinical characteristics of the study population (n=50).

	Basal
<b>Gender</b>	
- Males	21 (42.0%)
- Females	29 (58.0%)
<b>Age (years)</b>	
- Mean±SD	52.8±14.9
- Range	28 - 80
<b>Weight (kg)</b>	
- Mean±SD	71.6±12.7
- Range	47 - 98
<b>Height (cm)</b>	
- Mean±SD	168±11
- Range	149 - 191
<b>BMI (kg/m<sup>2</sup>)</b>	
- Mean±SD	25.2±3.2
- Range	17.9 - 32.4
<b>Weight status classes</b>	
Underweight (BMI<18.5 kg/m <sup>2</sup> )	1 (2.0%)
Normal weight (BMI between 18.5 and <25 kg/m <sup>2</sup> )	23 (46.0%)
Overweight (BMI between 25 and <30 kg/m <sup>2</sup> )	22 (44.0%)
Obese (BMI 30 kg/m <sup>2</sup> and above)	4 (8.0%)
<b>Use of antacid drugs</b>	3 (6.0%)



**Figure 1.** Presence of the 20-item symptoms of the PAGI-SYM questionnaire at baseline in the 50 patients admitted to the study.

## 2.5. Endpoints

The primary endpoint of the study was to evaluate the effectiveness of the intake of  $\geq 1.5$  L/day of bicarbonate mineral water for two weeks on the symptoms of GERD and in promoting digestive activity by significantly reducing the PAGA-SYM total score.

As secondary endpoints, we also evaluated the effect of the bicarbonate mineral water on: i) the subscales of the PAGA-SYM questionnaire; ii) the modification of the use of antacid drugs; and, iii) the patients' self-assessment of digestive effectiveness, as well as, the satisfaction with the treatments.

In addition, in the third two-week period, we also evaluated if the effect of bicarbonate mineral water may be maintained after the replacement of the intake with oligomineral water.

## 2.6. Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGA-SYM)

The PAGA-SYM was intended to cover the main symptom groupings for the following upper GI disorders: GERD, dyspepsia and gastroparesis for application in clinical trials and other studies. The content and items of the PAGA-SYM were constructed based on an extensive review of published medical literature, review of previously developed GI symptom scales, semi-structured interviews with patients, and interviews and meetings with experienced gastroenterologists. Subject interviews about GI symptoms and their effect on health-related quality of life were conducted in six countries (France, Germany, Italy, Poland, Sweden, and the United States). The items were developed to be linguistically and culturally appropriate for multinational studies.

The final PAGA-SYM questionnaire contains 20 items and 6 subscales covering heartburn/regurgitation (7 items), nausea/vomiting (3 items), post-prandial fullness/early satiety (4 items), bloating (2 items), upper abdominal pain (2 items), and lower abdominal pain (2 items). The scores of the items vary from 0 to 5: 0, "none" or "absent"; 1 "very mild"; 2 "mild", 3 "moderate", 4 "severe", and 5 "very severe". The PAGA-SYM subscale scores are calculated by taking the mean of the items in each subscale, while the total score is calculated by taking the mean of the subscales; thus, subscale and total scores also vary from 0 to 5 [30–32].

## 2.7. Antacid Intake

During the study, the use of antacids on demand was allowed and recorded and this represents a secondary endpoint of the study.

## 2.8. Patient Satisfaction

In addition to the PAGA-SYM questionnaire, at the end of each of the three treatment periods, patients were also asked to express an opinion on their satisfaction with the treatments using a 4-point Likert rating scale: "poor", "moderate", "good", and "very good".

Finally, an 1-to-10 scale was used to assess the patients' subjective digestive effectiveness. These opinions were recorded after the two periods of supplementation with both bicarbonate natural mineral water and oligomineral water.

## 2.9. Safety

Safety was assessed by recording the occurrence of adverse events.

## 2.10. Statistical Methods

### 2.10.1. Sample-Size Calculation

In order to evaluate the sample size of the present crossover pilot study, we hypothesized to be able to detect an improvement of dyspepsia and GERD symptoms similar to the changes observed after follow-up in the subset of subjects reporting symptom relief out of the population studied for the evaluation of the responsiveness of the PAGA-SYM questionnaire [30]. By considering the median change of the 6 subscales in subjects with both dyspepsia and/or GERD symptom relief (-0.54) with a

median SD of 1.13, [30] a sample size of 48 pairs is needed to be able to reject the null hypothesis with a probability (power) equal to 90% and a type I error of 5% according to the PS Power and Sample Size Calculations package (Version 3.1.2; Department of Statistics, Vanderbilt University, Nashville, TN, USA) [33,34]. Thus, we rounded this value and enrolled 50 subjects.

### 2.10.2. Statistical Analysis

The mean and standard deviation were reported as descriptive statistics for continuous variables, as well as absolute and relative frequencies, were reported for discrete variables. Non-parametric statistics were used in order to analyze the data. The Fisher's exact and the Mann-Whitney U tests were used to compare drop-out patients with participant patients according to dichotomous and ordinal variables, respectively. In the evaluation of the effects of the wash-out period and of the two natural mineral water administrations, as well as in their comparison, the Wilcoxon matched-pairs test was used to analyze ordinal variables, while McNemar and marginal homogeneity tests were used to analyze dichotomous responses and their modification, respectively. All data were managed and analyzed via the IBM SPSS Statistics (Ver. 23 for Windows, IBM Co., Armonk, NY, USA) package. Two-tailed P values of less than 0.05 were considered statistically significant.

### 2.11. Ethical Issues

The study protocol was approved by the Institutional Review Board of the "Water Resource Association" (Bologna, Italy). Because treatment consisted of the simple administration of tap and mineral waters only and there were no medical drugs or similar treatments, approval from an official Ethics Committee was not required.

The study protocol conforms to the ethics of the World Medical Association Declaration of Helsinki "Ethical principles for medical research involving human subjects", adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 75th WMA General Assembly, Helsinki, Finland, October 2024.

Only patients who voluntarily signed an informed consent were included, as well as, patients were allowed to discontinue participation at any time during the trial.

## 3. Results

### 3.1. Patients

Out of the 50 patients admitted to the study, there were 5 drop-outs (10.0%) (2 men and 3 women): 2 did not follow the instructions for the water intake and did not perform the initial wash-out with tap water correctly and 3 did not attend the visit after the wash-out period. Therefore, 45 subjects (90.0%) completed the study. No significant differences were found between drop-out patients and those who completed the study as far as gender ( $P=1.000$ ), age ( $P=0.571$ ), weight ( $P=0.264$ ), height ( $P=0.332$ ), BMI ( $P=0.528$ ), weight status classes ( $P=0.531$ ), and use of antacid drugs ( $P=0.276$ ) are concerned. On the other hand, drop-out patients had generally non-significantly higher basal PAGI-SYM subscales ( $P$  ranging from 0.056 to 0.334), but the heartburn/regurgitation subscale was significantly higher ( $P=0.026$ ) and the total PAGI-SYM score resulted at the significant level ( $P=0.050$ ).

### 3.2. Protocol Deviations and Compliance

No missing data were present in the compilation of the PAGI-SYM items; therefore, there was no need of applying the half-scale rule for missing data in calculating the subscales [31]. On the other hand, in 12 cases the items were double-filled and the higher score was chosen.

The length of the water intake was within the accepted range ( $14\pm 1$  day) in the 95.6% of cases, while it was of 16 days in 6 cases (4.4%; one during wash-out (0.7%), 5 during bicarbonate water (3.7%), and none during oligomineral water). Thus, the length of the water intake was significantly

shorter during wash-out ( $13.7\pm 0.7$  days) than during both bicarbonate water ( $14.4\pm 0.7$  days;  $P<0.001$ ) and oligomineral water ( $14.0\pm 0.1$ ;  $P=0.002$ ) as well as, it was longer during bicarbonate than oligomineral water ( $P=0.001$ ).

### 3.3. The Pagi-SYM Severity Index

Results of the Pagi-SYM severity index are shown in Table 5. At baseline, bloating, post-prandial fullness/early satiety and heartburn/regurgitation had the higher mean scores ranging between 1.75 and 2.16, while nausea/vomiting and lower abdominal pain had the lower ones (0.77 and 0.96, respectively). The mean total score was 1.47.

**Table 5.** Results of the Pagi-SYM severity index.

	Subscales of Pagi-SYM severity index						Pagi-SYM total score
	Heartburn / Regurgitation	Nausea / Vomiting	Post-prandial fullness / Early satiety	Bloating	Upper abdominal pain	Lower abdominal pain	
<b>Basal (T0)</b>							
Mean±SD	1.75±0.79	0.77±0.99	1.83±1.05	2.16±1.03	1.36±1.07	0.96±1.03	1.47±0.76
<b>After wash-out (T1)</b>							
Mean±SD	1.69±0.75	0.85±0.99	1.77±0.99	1.90±0.87	1.29±1.03	1.07±0.97	1.43±0.71
Effect (Difference vs. T0)	-0.06±0.23	0.08±0.24	-0.06±0.31	-0.26±0.39	-0.07±0.31	0.11±0.35	-0.04±0.15
P value <sup>a</sup>	0.116	0.026	0.164	<0.001	0.157	0.040	0.084
<b>After bicarbonate mineral water (T2)</b>							
Mean±SD	1.00±0.78	0.42±0.66	1.01±0.68	1.07±0.77	0.72±0.70	0.56±0.77	0.80±0.62
Effect (Difference vs. T1)	-0.69±0.55	-0.43±0.61	-0.76±0.69	-0.83±0.65	-0.57±0.64	-0.51±0.69	-0.63±0.48
P value <sup>a</sup>	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
<b>After oligomineral water (T3)</b>							
Mean±SD	1.44±0.70	0.79±0.86	1.51±0.73	1.47±0.97	1.24±0.97	0.97±0.89	1.24±0.69
Effect (Difference vs. T2)	0.45±0.50	0.36±0.57	0.50±0.47	0.40±0.81	0.52±0.83	0.41±0.71	0.44±0.50
P value <sup>a</sup>	$P<0.001$	$P<0.001$	$P<0.001$	0.001	$P<0.001$	$P<0.001$	$P<0.001$
<b>Bicarbonate vs. oligomineral water</b>							
Difference of the effects	-1.14±0.99	-0.79±1.09	-1.26±1.06	-1.23±1.26	-1.09±1.33	-0.92±1.34	-1.07±0.93
P value <sup>b</sup>	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$

<sup>a</sup> Changes observed vs. the previous visit (Wilcoxon matched-pair test). <sup>b</sup> Comparison between changes observed after bicarbonate mineral water vs. those observed after oligomineral water (Wilcoxon matched-pair test).

A highly significant decrease of the bloating subscale ( $P<0.001$ ) was found after the wash-out period, while nausea/vomiting and lower abdominal pain significantly increased ( $P=0.026$  and  $P=0.040$ , respectively). The decrease of the total score during wash-out did not reach statistical significance ( $P=0.084$ ).

All the six subscales, as well as the total score, significantly decreased ( $P<0.001$ ) after bicarbonate mineral water intake, while they significantly increased after oligomineral water supplementation ( $P<0.001$  for all scores but bloating with  $P=0.001$ ). Therefore, the comparison between the effects of the mineral waters showed significantly lower values of the bicarbonate one ( $P<0.001$ ) for all subscales, as well as for the total score.

### 3.4. Use of Antacid Drugs

Antacid use was reported by 3 out of the 50 patients at baseline (6.0%; 1 drop-out). In the 45 patients that completed the study, antacid use significantly ( $P<0.001$ ) increased from baseline (2 patients, 4.4%) to the end of the wash-out period (15 patients, 33.3%), and it further declined at the visit after bicarbonate mineral water intake (6 patients, 13.3%) (Table 6). The increases in the use of antacid drugs observed during the wash-out period was significant ( $P<0.001$ ) as well as the decrease observed after bicarbonate mineral water was significant ( $P=0.004$ ). On the other hand, an increase of

antacid use was found during the oligomineral water intake, but not reaching the significant level ( $P=0.070$ ). The comparison between the decrease of antacid use observed during bicarbonate mineral water (9 patients suspended antacids, 20.0%) *versus* the increase observed during oligomineral water (7 patients needed new antacid administration, 15.6%, while 1 patient only suspended antacid administration, 2.2%) was significant ( $P=0.005$ ).

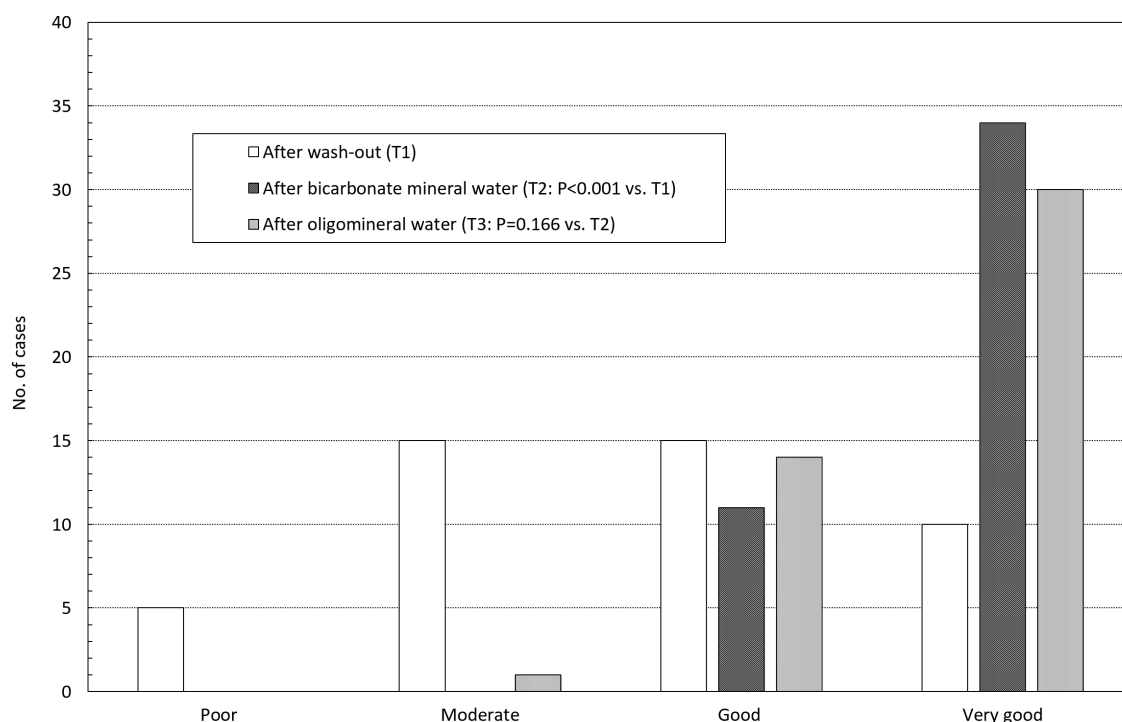
**Table 6.** Use of antacid drugs.

	No. of patients	P <i>vs.</i> previous visit <sup>a</sup>	Changes <i>vs.</i> previous visit		
			Suspension	Unchanged	New assumption
Basal (T0)	2 (4.4%)	-	-	-	-
After wash-out (T1)	15 (33.3%)	<0.001	-	32 (71.1%)	13 (28.9%)
After bicarbonate mineral water (T2)	6 (13.3%)	0.004	9 (20.0%)	36 (80.0%)	-
After oligomineral water (T3)	12 (26.7%)	0.070	1 (2.2%)	37 (82.2%)	7 (15.6%)

<sup>a</sup> McNemar test. <sup>b</sup> Comparison between changes observed during bicarbonate mineral water *versus* oligomineral water:  $P=0.005$  (Marginal homogeneity test).

### 3.5. Patient Satisfaction and Safety

The patients' opinion on their satisfaction with the treatments is shown in Figure 2. As far as the wash-out period is concerned, 25 patients (55.6%) had a positive opinion of the treatment (very good: 10, 22.2%; good: 15, 33.3%) while 15 patients (33.3%) rated it as moderate and 5 patients only (11.1%) rated it as poor. The patient satisfaction was significantly higher ( $P<0.001$ ) in comparison to the wash-out period for bicarbonate mineral water (all patients had a positive opinion: very good 34, 75.6%; good 11, 24.4%) while after oligomineral water (44 patients had a positive opinion, 97.8%: very good 30, 66.7%; good 14, 31.1%; and 1 patient only declared a moderate satisfaction, 2.2%) the comparison with bicarbonate mineral water was not statistically significant ( $P=0.166$ ).



**Figure 2.** Patients' opinion on their satisfaction with the treatment.

On the other hand, the results of the scale assessing the patient's subjective assessment of effectiveness of their digestion are shown in Table 7. The consumption of bicarbonate natural mineral water showed a significant ( $P < 0.001$ ) better score ( $7.2 \pm 2.2$ ) in comparison to the oligomineral water intake ( $4.6 \pm 2.0$ ).

**Table 7.** Patients' subjective assessment of efficiency of their digestion (Scale 1-10).

	Mean $\pm$ SD	Range
After bicarbonate mineral water (T2)	7.2 $\pm$ 2.2 <sup>a</sup>	2-10
After oligomineral water (T3)	4.6 $\pm$ 2.0 <sup>a</sup>	1-9

<sup>a</sup> Comparison between bicarbonate mineral water vs. oligomineral water:  $P < 0.001$  (Wilcoxon matched-pair test).

As far as safety is concerned, all the three water regimens were well tolerated, and no patients declared any adverse effect.

#### 4. Discussion

This first phase of the study investigated whether a two-week intake of a bicarbonate natural mineral water (Aqua 3) source could improve upper gastrointestinal symptoms in patients with FD and gastroesophageal reflux-related complaints and aid digestion. The results showed a significant reduction in all PAGA-SYM subscales and in the total symptom score after consumption of the bicarbonate water, accompanied by a parallel reduction in the use of antacid medications and a marked improvement in patients' subjective perception of digestive effectiveness. Importantly, these beneficial effects were not maintained after switching to an oligomineral water, during which symptoms significantly worsened and antacid use tended to increase, although less markedly. Together, these findings suggest that the bicarbonate mineral water exerts specific symptomatic benefits that cannot be attributed solely to increased hydration or to fluctuations in symptom severity over time.

The mechanisms underlying the observed effects are likely multifactorial and consistent with previous physiological and clinical research on bicarbonate-rich waters. Several studies have shown that bicarbonate and calcium ions can modulate gastric secretory pathways, stimulate endogenous gastrin release, enhance buffering of gastric acidity, and influence gastroduodenal motility [13,15,16]. Experimental models further support their role in promoting gastric emptying, modulating hepatobiliary secretion, and acting on intestinal transit. Our findings align with these mechanisms, given that the most responsive symptom dimensions in our cohort were post-prandial fullness, epigastric distress, and heartburn/regurgitation (domains that are biologically sensitive to changes in gastric acid, gastric motility, and duodenal buffering).

In fact, mineral waters, due to their composition in ions, macro and microelements, can stimulate the release or modulate the activity of some neurohumoral regulators of the digestive process [35–37]. Of particular interest are the effects of  $\text{Ca}^{2+}$  on the liberation of gastrin from antral G cells, [9] on exocrine pancreatic secretion, [38–40] on gastroduodenal bicarbonate secretion, and on the activity of intracellular cyclic nucleotides (cAMP and cGMP) on which the responses of functional effectors to exogenous or endogenous stimuli depend [10,41–43].  $\text{Mg}^{2+}$  generally exerts antagonistic actions against  $\text{Ca}^{2+}$ , has a relaxing effect on the sphincter of Oddi, and stimulates intestinal peristaltic motility [44,45]. The  $\text{SO}_4^{2-}$  anions stimulate the release of CCK from GEP endocrine cells and the secretion of  $\text{H}_2\text{O}$  and bicarbonates from enterocytes; the  $\text{HCO}_3^-$  anion performs a neutralizing action on gastric secretion [45,46].  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  influence, in relation to their respective concentrations, the membrane potential of the myocytes of the enteric wall, with possible implications for both postprandial and interdigestive motility. The therapeutic effect exerted by mineral waters in some diseases and disorders of the digestive system is the result of: i) quantitative and/or qualitative modifications of some basic digestive functions (motility, secretion, etc.); ii) actions aimed at counteracting and reducing pathological phenomena (inflammation and/or degenerative processes,

etc.); iii) general non-specific effects, such as the restoration of the hydro-electrolyte balance, and compensation for any acid-base homeostasis imbalances.

A highly relevant aspect of our study is the wash-out period, which allowed us to control for symptoms potentially related to insufficient hydration, a condition known to worsen dyspeptic symptoms in predisposed individuals. Although some improvement in bloating was observed during wash-out, no significant reduction in the overall PAGA-SYM score occurred, supporting the idea that hydration alone cannot explain the benefits observed with bicarbonate water. This methodological choice strengthens the internal validity of the study and contributes to the interpretation of the subsequent treatment effects.

The decision not to adopt a randomized cross-over design was deliberate (despite its methodological advantages) because no prior data existed on the behavior of the PAGA-SYM score after mineral water intake. A cross-over design would have risked introducing significant carry-over effects, especially given the hypotheses concerning prolonged physiological effects of bicarbonate waters on gastric secretion and motility. In this preliminary phase, the sequential design provided essential information to support the planning of a definitive randomized cross-over controlled trial. Nevertheless, the lack of randomization and the fixed sequence (bicarbonate first, oligomineral second) remains a limitation. It is possible that the second intervention (oligomineral water) suffered from a “floor effect,” as patients entered this phase with substantially reduced symptoms after the bicarbonate period. Although symptom worsening was nonetheless observed, a fully randomized cross-over design will be required to rule out sequence bias.

The rate of drop-outs was low, but most non-compliant subjects failed to complete the wash-out phase, preventing assessment of whether baseline severity differed between completers and non-completers. Nonetheless, compliance among study completers was excellent, and no missing data were present for PAGA-SYM scoring. The absence of objective physiological measurements (such as gastric emptying studies, pH-impedance monitoring, or hormone assays) also limits mechanistic interpretation. These parameters will be incorporated into the next phase of the project as prespecified objective endpoints.

## 5. Conclusions

In line with the evidence reported in the literature, the findings of this study provide additional support for recommending natural bicarbonate mineral water as a symptomatic treatment for FD and GERD. The intake of Aqua 3 bicarbonate mineral water proved to be a simple, safe, and natural intervention capable of improving digestive symptoms in patients with functional dyspepsia and reflux-related disorders, while promoting the digestive process. The concurrent improvement in perceived digestive effectiveness and the reduction in antacid use further reinforce its clinical relevance.

Given the chronic and fluctuating nature of functional dyspepsia and the limited effectiveness of available pharmacological therapies, the possibility of alleviating symptoms through a well-tolerated natural mineral water represents an option of significant clinical and public health interest, potentially reducing the economic burden on healthcare resources.

The recommendation to prescribe mineral water as an adjunctive treatment during the initial phase of therapy, or even as the sole agent for maintenance therapy, should be considered in patients with functional dyspepsia and/or GERD.

**Author Contributions:** Conceptualization, A.Z. and F.P.; methodology, A.Z. and F.P.; formal analysis, A.M.M.L.; investigation, A.Z., F.P. and A.A.I.; data curation, A.M.M.L.; writing original draft preparation, A.Z., F.P., G.Z. and A.M.M.L.; writing review and editing, A.Z., F.P., G.Z. and A.M.M.L. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional review board statement:** This study was conducted in accordance with the Declaration of Helsinki. The protocol study was approved by the Institutional Review Board of the “Water Resource Association” (Bologna, Italy; Code DS-1a/2025).

**Acknowledgments:** The authors thank Carpathian Springs S.A. (Vatra Dornei, Romania) for providing the water necessary for conducting this study.

**Conflicts of interest:** The authors declare no conflicts of interest.

## Abbreviations

EPS: epigastric pain syndrome; FD: functional dyspepsia; GERD: gastroesophageal reflux disease; GI: gastrointestinal; PDS: postprandial distress syndrome.

## References

1. Raynal C. La vente des eaux minérales par les pharmaciens. *Rev Hist Pharm (Paris)* 2004;344:587-606.
2. European Parliament. Directive 2009/54/EC of the European Parliament and of the Council of 18 June 2009 on the exploitation and marketing of natural mineral waters. Available at: <https://eur-lex.europa.eu/eli/dir/2009/54/oj/eng>.
3. European Parliament. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Available at: <https://eur-lex.europa.eu/eli/dir/2001/83/oj/eng>.
4. Zhixian S, Theng M, Zhang M, Rangan A. Water and beverage consumption: analysis of the Australian 2011-2012 National Nutrition and Physical Activity Survey. *Nutrients* 2016;8:678.
5. Drewnoski A, Rhem CD, Constant F. Water and beverage consumption among adults in the United States: cross-sectional study using data from NHANES 20. *BMC Public Health*. 2013;13:1068.
6. Gibson, S.; Shirreffs, S.M. Beverage consumption habits “24/7” among British adults: association with total water intake and energy intake. *Nutr. J.* **2013**, *12*, 9–9. <https://doi.org/10.1186/1475-2891-12-9>.
7. Petraccia, L.; Liberati, G.; Masciullo, S.G.; Grassi, M.; Fraioli, A. Water, mineral waters and health. *Clin. Nutr.* **2006**, *25*, 377–385. <https://doi.org/10.1016/j.clnu.2005.10.002>.
8. D’Souza A, Zink K, Langhorst J, Widner W, Stuopp C, Keill T. How effective is drinking natural mineral water against heartburn from functional dyspepsia, gastroesophageal reflux disease, or other causes? A systematic review of clinical intervention studies. *Complement Med Res* 2024;31:253-65.
9. Hearty RF, Maico DG, McGuigan EJ. Role of calcium in antral gastrin release. *Gastroenterology* 1981;80:491-7.
10. Flemström, G.; Garner, A. Stimulation of gastric acid and bicarbonate secretions by calcium in guinea pig stomach and amphibian isolated mucosa. *Acta Physiol. Scand.* **1980**, *110*, 419–426. <https://doi.org/10.1111/j.1748-1716.1980.tb06689.x>.
11. Layer P, Hotz J, Schmitz-Moormann HP, Goebell H. Effects of experimental chronic hypercalcemia on exocrine pancreatic enzyme secretion by intravenous calcium infusion in rats: inhibition by atropine. *Gastroenterology* 1979;76:1181.
12. Pace, F.; Morselli-Labate, A.M.; Abu Issa, A.; Zanasi, A. Bicarbonate Natural Mineral Water from Source “F2 Păltiniș” Facilitates Digestion—A Pilot Study. *Gastrointest. Disord.* **2025**, *7*, 47. <https://doi.org/10.3390/gidisord7030047>.
13. Bertoni, M.; Oliveri, F.; Manghetti, M.; Boccolini, E.; Bellomini, M.G.; Blandizzi, C.; Bonino, F.; DEL Tacca, M. EFFECTS OF A BICARBONATE-ALKALINE MINERAL WATER ON GASTRIC FUNCTIONS AND FUNCTIONAL DYSPEPSIA: A PRECLINICAL AND CLINICAL STUDY. *Pharmacol. Res.* **2002**, *46*, 525–531. <https://doi.org/10.1016/s1043661802002323>.
14. Labenz, J.; Anschütz, M.; Walstab, J.; Wedemeyer, R.-S.; Wolters, H.; Schug, B. Heartburn relief with bicarbonate-rich mineral water: results of the randomised, placebo-controlled phase-III trial STOMACH STILL. *BMJ Open Gastroenterol.* **2023**, *10*, e001048. <https://doi.org/10.1136/bmjgast-2022-001048>.
15. Quattrini, S.; Pampaloni, B.; Brandi, M.L. Natural mineral waters: chemical characteristics and health effects. *Bone Abstr.* **2016**, *13*, 173–180. <https://doi.org/10.11138/ccmbm/2016.13.3.173>.

16. Cuomo, R.; Grasso, R.; Sarnelli, G.; Capuano, G.; Nicolai, E.; Nardone, G.; Pomponi, D.; Budillon, G.; Ierardi, E. Effects of carbonated water on functional dyspepsia and constipation. *Eur. J. Gastroenterol. Hepatol.* **2002**, *14*, 991–999. <https://doi.org/10.1097/00042737-200209000-00010>.
17. Lee, D.; Hong, J.H. The Fundamental Role of Bicarbonate Transporters and Associated Carbonic Anhydrase Enzymes in Maintaining Ion and pH Homeostasis in Non-Secretory Organs. *Int. J. Mol. Sci.* **2020**, *21*, 339. <https://doi.org/10.3390/ijms21010339>.
18. Grassi, M.; Fraioli, A.; Pappalardo, G.; Messina, B.; Belardinelli, L.; Guadalaxara, A. [Alkalinizing activity of a calcium-bicarbonate-containing water, evaluated for pH, in patients with gastroesophageal reflux]. **1993**, *143*, 131–6.
19. Bortolotti, M.; Turba, E.; Mari, C.; Lopilato, C.; Porrazzo, G.; Scalabrino, A.; Miglioli, M. [Changes caused by mineral water on gastrointestinal motility in patients with chronic idiopathic dyspepsia]. **2000**, *90*, 187–94.
20. Barclay, G.; Maxwell, V.; Grossman, M.I.; Solomon, T.E. Effects of graded amounts of intragastric calcium on acid secretion, gastrin release, and gastric emptying in normal and duodenal ulcer subjects. *Dig. Dis. Sci.* **1983**, *28*, 385–391. <https://doi.org/10.1007/bf02430525>.
21. Fornai M, Antonioli L, Colucci R, Tuccori M, Awwad O, Serra M, et al. Role of crenotherapy with mineral waters in the treatment of functional disorders of digestive tract. *Gazz Med Ital* 2012;171:213-26.
22. Walsh JH. Gastrointestinal peptide hormones. In: *Gastrointestinal disease (patophysiology, diagnosis, management)*. Sleisenger MH, Fordtran JS. Philadelphia: Eds. Saunders; 1983. p.54.
23. Gasbarrini, G.; Candelli, M.; Graziosetto, R.G.; Coccheri, S.; Di Iorio, F.; Nappi, G. Evaluation of thermal water in patients with functional dyspepsia and irritable bowel syndrome accompanying constipation. *World J. Gastroenterol.* **2006**, *12*, 2556–2562. <https://doi.org/10.3748/wjg.v12.i16.2556>.
24. Fornai, M.; Colucci, R.; Antonioli, L.; Ghisu, N.; Tuccori, M.; Gori, G.; Blandizzi, C.; Del Tacca, M. Effects of a bicarbonate-alkaline mineral water on digestive motility in experimental models of functional and inflammatory gastrointestinal disorders. *Methods Find. Exp. Clin. Pharmacol.* **2008**, *30*, 261–9. <https://doi.org/10.1358/mf.2008.30.4.1159650>.
25. Kurata, J.H.; Nogawa, A.N.; Everhart, J.E. A Prospective Study of Dyspepsia in Primary Care. *Dig. Dis. Sci.* **2002**, *47*, 797–803. <https://doi.org/10.1023/a:1014748202229>.
26. Chuah, K.H.; Cheong, S.Y.; Lim, S.Z.; Mahadeva, S. Functional dyspepsia leads to more healthcare utilization in secondary care compared with other functional gastrointestinal disorders. *J. Dig. Dis.* **2022**, *23*, 111–117. <https://doi.org/10.1111/1751-2980.13082>.
27. Stanghellini V, Chan FK, Hasler WL, Malagelada JR, Suzuki H, Tack J, et al. Gastrointestinal disorders. *Gastroenterology* 2016;150:1380-92.
28. Dragomireska NV, Iliescu MG, Mazilu L, Micu SI, Suceveanu AP, Voinea F, et al. Application of mineral waters in the complex treatment of patients with gastroesophageal reflux disease. *Minerva Gastroenterol Dietol* 2020;66:225-7.
29. Dumitrescu, M.; Iliescu, M.G.; Mazilu, L.; Micu, S.I.; Suceveanu, A.P.; Voinea, F.; Voinea, C.; Stoian, A.P.; Suceveanu, A.-I. Benefits of crenotherapy in digestive tract pathology (Review). *Exp. Ther. Med.* **2021**, *23*, 1–5. <https://doi.org/10.3892/etm.2021.11045>.
30. Revicki, D.A.; Rentz, A.M.; Tack, J.; Stanghellini, V.; Talley, N.J.; Kahrilas, P.; de la Loge, C.; Trudeau, E.; Dubois, D. Responsiveness and interpretation of a symptom severity index specific to upper gastrointestinal disorders. *Clin. Gastroenterol. Hepatol.* **2004**, *2*, 769–777. [https://doi.org/10.1016/s1542-3565\(04\)00348-9](https://doi.org/10.1016/s1542-3565(04)00348-9).
31. Rentz, A.; Kahrilas, P.; Stanghellini, V.; Tack, J.; Talley, N.; De la Loge, C.; Trudeau, E.; Dubois, D.; Revicki, D. Development and psychometric evaluation of the patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM) in patients with upper gastrointestinal disorders. *Qual. Life Res.* **2004**, *13*, 1737–1749. <https://doi.org/10.1007/s11136-004-9567-x>.
32. Kindt, S.; Dubois, D.; Van Oudenhove, L.; Caenepeel, P.; Arts, J.; Bisschops, R.; Tack, J. Relationship between symptom pattern, assessed by the PAGI-SYM® questionnaire, and gastric sensorimotor dysfunction in functional dyspepsia. *Neurogastroenterol. Motil.* **2009**, *21*, 1183–e105. <https://doi.org/10.1111/j.1365-2982.2009.01374.x>.

33. Dupont, W.D. Power Calculations for Matched Case-Control Studies. *Biometrics* **1988**, *44*, 1157–1168. <https://doi.org/10.2307/2531743>.
34. Dupont, W.D.; Plummer, W.D. P-58 Power and sample size calculations: A review and computer program. *Control. Clin. Trials* **1990**, *11*, 301. [https://doi.org/10.1016/0197-2456\(90\)90157-w](https://doi.org/10.1016/0197-2456(90)90157-w).
35. Grassi, M.; Fraioli, A. [Gastroenteropancreatic endocrine system and crenotherapy with mineral waters]. **1988**, *127*, 379–84.
36. Maltinti G, Polloni A, Marchi S, Costa F, Bellini M, Guglielmini R. Influenza degli ioni sull'assetto enterormonale. *Clin Term* 1988; 41:129.
37. Kuznetsov, B.G. [Gastroenteropancreatic endocrine system and its role in the mechanism of action of potable mineral waters (a review of the literature)]. **1981**, 63–7.
38. Layer, P.; Hotz, J.; Schmitz-Moormann, H.; Goebell, H. Effects of experimental chronic hypercalcemia on feline exocrine pancreatic secretion. *Gastroenterology* **1982**, *82*, 309–316. [https://doi.org/10.1016/0016-5085\(82\)90020-8](https://doi.org/10.1016/0016-5085(82)90020-8).
39. Hotz, J.; Goebell, H.; Ziegler, R. Interactions of calcium, magnesium and atropine on exocrine pancreatic secretion in man. *Eur. J. Clin. Investig.* **1978**, *8*, 303–307. <https://doi.org/10.1111/j.1365-2362.1978.tb00846.x>.
40. Inoue, K.; Fried, G.M.; Wiener, I.; Sakamoto, T.; Lilja, P.; Greeley, G.H.; Watson, L.C.; Thompson, J.C. Effect of divalent cations on gastrointestinal hormone release and exocrine pancreatic secretion in dogs. *Am. J. Physiol. Liver Physiol.* **1985**, *248*, G28–G34. <https://doi.org/10.1152/ajpgi.1985.248.1.g28>.
41. Flemstrom G. Effect of catecholamines, Ca<sup>++</sup> and gastrin on gastric HCO<sub>3</sub> secretion. *Acta Physiol Scand* 1978 (Suppl. Gastric Ion Transport);81:90.
42. Grassi M, Messina B, Fraioli A. La secrezione di bicarbonato a livello gastroduodenale. Aspetti di fisiopatologia digestiva e di terapia. *Clin Ter* 1985;115:113-7.
43. Schwartz, C.J.; Kimberg, D.V.; Sheerin, H.E.; Field, M.; Said, S.I. Vasoactive Intestinal Peptide Stimulation of Adenylate Cyclase and Active Electrolyte Secretion in Intestinal Mucosa. *J. Clin. Investig.* **1974**, *54*, 536–544. <https://doi.org/10.1172/jci107790>.
44. Christiansen, J.; Rehfeld, J.F.; Kirkegaard, P. Interaction of Calcium, Magnesium, and Gastrin on Gastric Acid Secretion. *Gastroenterology* **1979**, *76*, 57–61. [https://doi.org/10.1016/s0016-5085\(79\)80128-6](https://doi.org/10.1016/s0016-5085(79)80128-6).
45. Inoue K, Wiener I, Fagan CJ, Watson LC, Thompson JC. Correlation between gallbladder size and release of CCK after oral magnesium sulphate in man. *Ann Surg* 1983;197:412-5.
46. Kivilaakso, E. Contribution of Ambient HCO<sub>3</sub><sup>-</sup> to Mucosal Protection and Intracellular pH in Isolated Amphibian Gastric Mucosa. *Gastroenterology* **1983**, *85*, 1284–1289. [https://doi.org/10.1016/s0016-5085\(83\)80008-0](https://doi.org/10.1016/s0016-5085(83)80008-0).

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.